FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Tuesday, February 9, 2021

10:00 a.m. to 2:35 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Chen, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Philip C. Hoffman, MD

(Chairperson)

Professor of Medicine

The University of Chicago

Section of Hematology/Oncology

Department of Medicine

Chicago, Illinois

Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

David E. Mitchell

(Consumer Representative)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

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Global Regulatory Portfolio Lead, Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

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Professor of Gynecology and Obstetrics

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Daniel F. Hayes, MD, FASCO, FACP

Stuart B. Padnos Professor of Breast Cancer Research

University of Michigan Rogel Cancer Center

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Stan Lipkowitz, MD, PhD

Chief, Women's Malignancies Branch

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Memorial Sloan Kettering Cancer Center

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. HOFFMAN: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Philip Hoffman, and I will be chairing today's meeting. I will now call the February 9, 2021 meeting of the Oncologic Drugs Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHEN: Good morning. My name is She-Chia Chen, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Let's start with Dr. Halabi.

(No response.)

DR. CHEN: Dr. Halabi?

DR. HALABI: Yes. Good morning, everyone. This is Susan Halabi. I'm a statistician at Duke University.

DR. CHEN: Dr. Hoffman?

DR. HOFFMAN: My name is Philip Hoffman. I'm a medical oncologist at the University of Chicago.

DR. CHEN: Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative to the ODAC, and I'm also a multiple myeloma patient.

DR. CHEN: Dr. Armstrong?

DR. ARMSTRONG: My name is Deb Armstrong. I'm a medical oncologist at Johns Hopkins, a former member of ODAC, and former ODAC chair.

DR. CHEN: Dr. Ellis?

DR. ELLIS: My name is Matthew Ellis. I'm director of the Lester and Sue Smith Breast Center at Baylor College of Medicine in Houston, Texas.

DR. CHEN: Dr. Hayes?

DR. HAYES: I'm Dr. Daniel Hayes. I'm a medical oncologist and breast cancer expert at the University of Michigan.

DR. CHEN: Dr. Lipkowitz?

DR. LIPKOWITZ: My name is Stan Lipkowitz. I'm a medical oncologist and head of the Women's Malignancies Branch at the National Cancer Institute intramural program.

DR. CHEN: Dr. Portis?

DR. COMPAGNI PORTIS: Yes. This is Natalie Compagni Portis, and I'm the patient representative for today's meeting.

DR. CHEN: Dr. Seidman?

DR. SEIDMAN: This is Dr. Andrew Seidman. I'm a breast medical oncologist at Memorial Sloan Kettering Cancer Center.

DR. CHEN: Dr. Wolff?

DR. WOLFF: My name is Dr. Antonio Wolff. I am a breast medical oncologist at Johns Hopkins University in Baltimore.

DR. CHEN: Dr. Kraus?

DR. KRAUS: Hi. Yes. I'm Albert Kraus.

I'm a global regulatory portfolio lead in oncology. I work with Pfizer to bring new drugs to patients, and I'm the industry representative today. Thank you.

DR. CHEN: Next are our FDA participants. We'll start with Dr. Pazdur.

DR. PAZDUR: Hi. This is Rick Pazdur. I'm the director of the Oncology Center of Excellence at the FDA.

DR. CHEN: Dr. Beaver?

DR. BEAVER: Hi. I'm Julia Beaver. I'm acting deputy director in the Office of Oncologic Diseases and chief of medical oncology in the Oncology Center of Excellence at FDA.

DR. CHEN: Dr. Amiri?

DR. AMIRI-KORDESTANI: Hi. This is Laleh Amiri. I'm a hematologist/oncologist. I'm the director of the Division of Oncology 1.

DR. CHEN: Dr. Osgood?

DR. OSGOOD: Hi. This is Christy Osgood. I am the clinical team leader from the FDA in the Division of Oncology Products 1.

DR. CHEN: Dr. Shah?

DR. SHAH: Good morning. My name is Mirat Shah, and I'm a medical oncologist and a clinical reviewer on the Breast and Gyn Malignancies Team within the Division of Oncology 1 at the FDA.

DR. CHEN: Dr. Fiero?

DR. FIERO: Hi. This is Mallorie Fiero. I am the statistical team leader in the Office of Biostatistics, supporting the Division of Oncology 1.

DR. CHEN: And Dr. Amatya.

DR. AMATYA: Hi. This is Anup Amatya. I am the statistical reviewer at FDA. Thank you.

DR. HOFFMAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if

recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during the break. Thank you.

Dr. She-Chia Chen will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHEN: The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest

or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of supplemental biologics license application, sBLA, 125514/s-089, for Keytruda, pembrolizumab, submitted by Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company Incorporated. The proposed indication use for this product is for the treatment of patients with high-risk, early-stage,

triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, then as a single agent as adjuvant treatment after surgery.

This is a particular matters meeting during which specific matters related to Merck's sBLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 (b)(3) to Drs. Deborah Armstrong; Matthew Ellis; Antonio Wolff; and Philip Hoffman.

Dr. Armstrong's waiver involves two of her employers' current research contracts for studies involving pembrolizumab. The study is funded by Translational Research in Oncology and University of California, Los Angeles, for which her employer receives $0 to $50,000 dollars annually and Dr. Armstrong receives $0 to $5,000 dollars annually in salary support.

The second study is funded by Merck Sharp & Dohme, a subsidiary of Merck & Company, and

University of Virginia, for which her employer receives $0 to $50,000 annually and Dr. Armstrong receives $0 to $5,000 annually in salary support.

Dr. Ellis' waiver involved his investment holdings in a healthcare sector mutual fund.

Dr. Wolff's waiver involves his investment holdings in a healthcare sector mutual fund

Dr. Hoffman's waiver involves his employer's current research contract for a study on pembrolizumab, sponsored by Merck & Company, for which his employer received $0 to $50,000 annually.

The waivers allow these individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests

may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Albert Kraus is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial

relationships that they may have with the firm at issue. Thank you.

DR. HOFFMAN: We will proceed with FDA introductory comments from Dr. Christy Osgood.

FDA Introductory Comments – Christy Osgood

DR. OSGOOD: Good morning, and welcome to the Oncologic Drugs Advisory Committee, or ODAC, meeting. I would like to thank all the committee members for attending and providing your advice today.

My name is Christy Osgood, and I am a pediatric oncologist and the cross-disciplinary team leader for the Biologics Licensing Application 125514 Supplement 89, for pembrolizumab. This application was submitted by Merck, who I will refer to as the applicant for the remainder of the presentation. I will be providing an introduction to the application and the issues that the FDA is requesting the committee to consider.

The applicant has proposed the following indication. Pembrolizumab is indicated for the

treatment of patients with high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then as a single agent for adjuvant treatment following surgery.

The applicant seeks an accelerated approval for the neoadjuvant and adjuvant treatment of early-phase, triple-negative breast cancer, or TNBC, based on demonstration of an improvement in pathological complete response, or pCR rate, and event-free survival, or EFS, result from interim analysis 3, or IA3.

pCR has not been established as an endpoint indicative of clinical benefit due to the uncertainty regarding its relationship to EFS and overall survival, or OS, which are established endpoints of clinical benefit.

For a drug to receive an accelerated approval for neoadjuvant therapy, the FDA considers the magnitude in pCR rate improvement and the acceptability of the added toxicity in a group of patients with a potentially curable disease.

Furthermore, compelling data of clinical benefit from another treatment setting in the same disease may mitigate some of the uncertainties surrounding the pCR endpoint.

To date, only one product, pertuzumab, a HER2-targeted monoclonal antibody, has been granted accelerated approval for neoadjuvant treatment based on an 18 percent improvement in pCR rate, as well as supportive efficacy data in the metastatic setting.

The applicant submitted interim results from KEYNOTE-522 to support their proposed indication. KEYNOTE-522 is a randomized, double-blind, placebo-controlled trial comparing pembrolizumab to placebo in combination with chemotherapy in the neoadjuvant setting and as monotherapy in the adjuvant setting in 1,174 patients with high-risk, early-stage, triple-negative breast cancer. The co-primary endpoints are pCR rate and EFS, and OS is a key secondary endpoint.

As pCR rate is measured at the time of surgery, it only captures the effect of the

neoadjuvant portion of treatment, not the adjuvant portion. In contrast, EFS and OS incorporate the effect of the entire neoadjuvant and adjuvant treatment regimen.

At the most recent analysis, IA3, the pCR rate difference between the two treatment arms was 7.5 percent with 95 percent confidence intervals of 1.6 percent to 13.4 percent, based on all randomized patients. At IA3, EFS had not met its prespecified threshold for statistical significance and remains immature with 53 percent of targeted EFS events having occurred.

Interim analysis may overestimate the treatment effect, particularly when the number of events is small. The data are not sufficiently mature for FDA to consider these interim EFS results as a reliable estimate of the EFS treatment effect, and further follow-up is needed.

Additionally, because EFS was not statistically significant, the OS endpoint could not be formally tested and is also immature with 32 percent of the targeted events having occurred.

Many patients with high-risk, early-stage TNBC will be cured with standard therapy, and therefore the added toxicity of pembrolizumab for neoadjuvant and adjuvant treatment must be carefully considered.

Results from KEYNOTE-522 showed that 43 percent of patients who received pembrolizumab experienced an immune-mediated adverse event compared to 22 percent of patients who received placebo.

Some immune-mediated adverse events experienced by the patients who received pembrolizumab were higher grade and resulted in hospitalization. Some of these toxicities, particularly those with endocrine dysfunction, may be irreversible or require lifelong medications in patients who will be cured of their breast cancer. Additionally, 4 deaths, potentially due to immune-mediated adverse events, occurred in patients receiving pembrolizumab.

Finally, although there were fewer immune-mediated adverse events during the adjuvant phase, these toxicities are still concerning because this

portion of the treatment regimen has not demonstrated a significant improvement on any long-term efficacy endpoints and may be adding risk without benefit.

Given these issues, it is not clear whether available data are reasonably likely to translate into improved outcomes for patients with high-risk, early-stage TNBC. There is uncertainty regarding the risk-benefit of neoadjuvant an adjuvant pembrolizumab, given the questionable clinical meaningfulness of a small improvement in pCR rate, the immaturity of the EFS and OS data, and increased immune-mediated toxicity.

Given this questionable clinical meaningfulness of the pCR rate improvement and the uncertainty of the EFS and OS data, the FDA has discouraged the applicant from submitting this application on two prior occasions.

Additionally, KEYNOTE-522 is an ongoing trial with multiple additional interim analyses planned and the final analysis. During a May 2020 meeting of the applicant's external data monitoring

committee, or DMC, it was recommended that KEYNOTE-522 continue without change as the EFS endpoint was not met at IA3. This further follow-up recommended by the DMC is necessary to characterize whether there is a clinical benefit of neoadjuvant and adjuvant pembrolizumab.

The FDA has identified the following five key issues for the ODAC to consider for BLA 125514 Supplement 89.

Neoadjuvant pembrolizumab confers only a small absolute improvement in pCR rate, which is of questionable clinical meaningfulness.

EFS and OS data are immature and unreliable.

The design and results of KEYNOTE-522 do not currently support a role for adjuvant pembrolizumab.

Support of data of clinical benefit from another TNBC treatment setting are lacking.

The addition of pembrolizumab is associated with increased toxicity due to increased immune-mediated adverse events, some of which may be severe, irreversible, and/or require lifelong

medication in potentially curable and otherwise healthy patients.

Based on this information and the key issues identified, FDA will ask the ODAC to vote on the following question.

Should a regulatory decision on pembrolizumab in combination with multi-agent chemotherapy for neoadjuvant treatment, followed by pembrolizumab monotherapy for adjuvant treatment of high-risk, early-stage TNBC, be deferred until further data are available from future analyses of KEYNOTE-522?

The FDA would like the ODAC members to comment on whether they think there is evidence of benefit to outweigh the risks of the pembrolizumab neoadjuvant and adjuvant treatment regimen at this time or whether we should await further data on long-term outcomes, including EFS and OS from future interim analyses, before making a regulatory decision. It is important to note that the results from the next interim analysis will be available in the second half of 2021.

Thank you, and I look forward to an interesting discussion.

DR. HOFFMAN: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the Merck Sharp & Dohme's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your presentation, it will not preclude you from speaking.

We will now proceed with presentations from Merck Sharp & Dohme Corporation, immediately followed by FDA presentation.

Applicant Presentation – Sunita Zalani

DR. ZALANI: Good morning, members of the FDA and Oncology Drugs Advisory Committee. My name is Sunita Zalani, and I'm vice president in the oncology therapeutic area and Global Regulatory Affairs and Safety at Merck. It's a pleasure to be here today to present to you the data in support of our supplemental BLA for pembrolizumab for the treatment of patients with high-risk, early-stage, triple-negative breast cancer or TNBC.

Keytruda, or pembrolizumab, is a highly selective humanized, monoclonal antibody that binds to PD-1 and blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2, thereby enhancing the anti-tumor immune response.

To date, U.S. FDA has approved pembrolizumab in 17 tumor types. Notably, pembrolizumab has been

approved in combination with platinum-based chemotherapy in several indications, as shown in green text, including most recently an accelerated approval in locally recurrent unresectable or metastatic TNBC.

KEYNOTE-522 is an ongoing phase 3, randomized double-blind study evaluating pembrolizumab plus chemotherapy versus placebo plus chemotherapy prior to surgery, followed by pembrolizumab monotherapy or placebo after surgery. KEYNOTE-522 was specifically designed to evaluate the short-term pathologic complete response and long-term event-free survival benefit of the entire regimen in the same population in the same study.

Based on results of KEYNOTE-522, we are seeking approval for the following indications. Keytruda is indicated for the treatment of patients with high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, then as a single agent as adjuvant treatment after surgery. We are requesting accelerated approval based on endpoints

that are reasonably likely to predict clinical benefit. Confirmatory studies are ongoing to convert to regular approval.

This time line illustrates the key regulatory milestones. The design of KEYNOTE-522 co-primary endpoints of pCR and EFS were reviewed with FDA in 2016, prior to study initiation. In 2017, FDA granted breakthrough therapy designation for this setting.

The marketing application was submitted in May 2020. Following discussions with FDA, data from the recent interim analysis 3 are included in this presentation. Our key topic for discussion at this ODAC is whether the magnitude of pCR response and EFS results support accelerated approval of pembrolizumab in the neoadjuvant and adjuvant setting for patients with high-risk, early-stage TNBC.

Today we will discuss the unmet need in patients with high-risk, early-stage TNBC. We will then present data from KEYNOTE-522, demonstrating that the study met its prespecified primary

endpoint.

Treatment with pembrolizumab in combination with chemotherapy produced a statistically significant improvement in pCR. The pCR data are further supported by a promising effect on EFS with a well-characterized and generally manageable safety profile. Lastly, we will address the totality of evidence supporting benefit-risk in this population.

The agenda for the sponsor presentation is as follows. Dr. Joyce O'Shaughnessy, a distinguished breast cancer expert and clinical trialist from Baylor University Medical Center, will present the disease background and unmet need. Dr. Vassiliki Karantza from Merck oncology will present the efficacy and safety data from KEYNOTE-522, and we will conclude with Dr. Hope Rugo, also a breast cancer expert and experienced clinical trialist from the University of California, San Francisco, who will provide her clinical perspective.

Dr. Vicki Goodman, vice president of

oncology development at Merck, will moderate the question and answer session. In addition, Dr. Aditya Bardia from Massachusetts General Hospital and Dr. Don Berry from the University of Texas MD Anderson Cancer Center will be available to answer your questions. We look forward to a productive dialogue.

Now I would like to turn the presentation over to Dr. O'Shaughnessy.

Applicant Presentation – Joyce O'Shaughnessy

DR. O'SHAUGHNESSY: Good morning. I'm Joyce O'Shaughnessy from Baylor University Medical Center, Texas Oncology and US Oncology in Dallas, Texas. It's my pleasure to describe for you the treatment landscape and unmet medical need in triple-negative breast cancer. I'm a paid consultant from Merck and I have no other financial interest in the outcome of this meeting.

Triple-negative breast cancer, or TNBC, is a virulent subtype of breast cancer associated with early onset and an increased risk of early recurrence. TNBC comprises about 15 to 20 percent

of breast cancers. Premenopausal and African American women are at higher risk of developing this subtype.

At diagnosis, the majority of triple-negative breast cancers are histologically grade 3 and highly proliferative, and most are diagnosed as stage 2 or stage 3 disease. And TNBC generally recurs quickly in the first 1 to 3 years following diagnosis in lungs, liver, and brain.

Stage for stage, TNBC, in the black curve, is associated with shorter overall survival compared with other breast cancer subtypes, despite the use of anthracycline and taxane-based systemic chemotherapy given in the curative setting. Overall, the 5-year survival rate for TNBC is about 77 percent compared with 93 percent for the other breast cancer subtypes.

Patients with stage 2 or 3 TNBC are considered at high risk for recurrence of advanced metastatic disease after definitive surgery. Those with stage 3 disease have a poor prognosis with a 4-year breast cancer specific survival rate of

about 50 percent, and those with stage 4 disease have a particularly poor outcome with a median survival of about 1 year and a 4-year survival rate of about 10 percent.

Shown here are the mature 5-year, event-free and overall survival rates updated in 2019 from the CALGB 40603 study of standard of care in neoadjuvant chemotherapy in patients with stage 2 or 3 TNBC. Patients in KEYNOTE-522 also had stage 2 or 3 disease, and these curves illustrate the substantial unmet need that these patients have even with state-of-the-art therapy, with 30 percent of patients developing disease recurrence by 3 years.

Chemotherapy is the mainstay of treatment in the curative setting, and the NCCN and ESMO guidelines recommend neoadjuvant regimens, including doxorubicin and cyclophosphamide, followed by a taxane or docetaxel and cyclophosphamide.

Taxane, anthracycline-based regimens are commonly used in clinical practice and generally

result in pathologic complete response rates in the breast and axillary lymph nodes in the range of 30 to 40 percent. The addition of carboplatin to taxane, anthracycline-based neoadjuvant chemotherapy increases the pathological complete response rates to approximately 50 percent.

Improving the pathologic complete response rate is very important in early-stage, triple-negative breast cancer because patients with residual disease at definitive surgery have a much worse prognosis.

Shown here are two studies demonstrating that patients who achieve a path CR with preoperative chemotherapy have substantially improved disease-free survival. On the left is the Cortazar meta-analysis from 2014 and on the right are data from CALGB 40603.

Both studies showed that patients who do not obtain a pathologic completely response have a very poor 5-year disease-free survival rate of only 50 to 60 percent, while those with a path CR have about an 85 percent disease-free survival rate at

5 years. Of note, despite having a path CR, these patients have a 15 percent persistent risk of disease recurrence.

The association between path CR and event-free survival is strongest in triple-negative breast cancer as demonstrated by these data sets. Based on these and other data, regulatory guidance supports the use of path CR as an endpoint for accelerated approval of neoadjuvant therapy in high-risk, early-stage breast cancer, including triple-negative breast cancer.

Turning now to immunotherapy, this slide outlines the rationale for use of immunotherapy in TNBC. PD-L1 is expressed in a higher proportion of triple-negative breast cancers, in general about 50 percent, compared with 20 to 30 percent in other breast cancer subtypes, and in high-risk, early-stage TNBC, PD-L1 expression is observed in approximately 85 percent of tumors.

A greater proportion of TNBCs contain tumor infiltrating lymphocytes, approximately 70 percent, compared with 25 to 44 percent for the other breast

cancer subtypes; and in the I-SPY2 trial, immune cell infiltrates were associated with path CR with neoadjuvant pembrolizumab.

There was also a strong biologic and clinical rationale for combining immunotherapy with chemotherapy. Chemotherapy results in tumor lysis, increased antigen shedding, and antigen presentation. It's also been shown that preoperative chemotherapy can result in increased expression of PD-L1.

Two recent clinical trials in triple-negative breast cancer patients, KEYNOTE-173 and I-SPY2, have shown that adding pembrolizumab to standard neoadjuvant chemotherapy results in high path CR rates of about 60 percent in both trials.

In summary, patients with high-risk, early-stage, triple-negative breast cancer have a worse prognosis compared with other subtypes, and patients with stage 2 or 3 breast cancer have an unacceptably high risk of recurrence and death with current standard chemotherapy regimens. Platinum-containing neoadjuvant regimens are

associated with the highest reported pathologic complete response rates of about 50 percent.

The short-term goal of neoadjuvant therapy is to achieve a pathologic complete response because a path CR is associated with improved event-free and overall survival. The long-term goal of neoadjuvant plus adjuvant therapy in TNBC is to prevent recurrence of incurable metastatic disease.

In TNBC, a recurrence avoided is a death of avoided. Therefore, there was a high unmet need for novel therapies that can augment the effectiveness of established chemotherapy in terms of preventing recurrence. And finally, there's a strong rationale for combining immunotherapy and chemotherapy in triple-negative breast cancer patients, and clinical trials have shown that pembrolizumab substantially improves path CR rates when combined with standard neoadjuvant chemotherapy.

Thank you, and I'll now turn the presentation over to Dr. Karantza.

Applicant Presentation – Vassiliki Karantza

DR. KARANTZA: Thank you, Dr. O'Shaughnessy.

I am Vassiliki Karantza, and I am the clinical lead for the breast program at Merck. This morning I will review the efficacy and safety results from KEYNOTE-522 and supportive data for this filing.

Merck's clinical development program in high-risk, early-stage TNBC involves four studies that enrolled more than 2200 patients and tested pembrolizumab in combination with different neoadjuvant chemotherapy regimens. Today we will focus on the randomized placebo-controlled phase 3 trial known as KEYNOTE-522, which is supported by data from I-SPY2 and the proof-of-concept study, KEYNOTE-173.

In addition, we are conducting a randomized phase 3 trial, KEYNOTE-242, that is testing pembro versus observation as adjuvant therapy for patients who did not have a pathological complete response.

Supportive of the KEYNOTE-522 filing is KEYNOTE-355, which is a randomized

placebo-controlled phase 3 study of pembrolizumab, plus chemotherapy compared to chemotherapy as first-line treatment for metastatic TNBC. That study showed a statistically significant and clinically meaningful improvement in progression-free survival among patients with PD-L1 positive tumors as measured by a combined positive score greater than or equal to 10.

Shown here is the design of KEYNOTE-522 that tested the addition of one year of pembrolizumab, given before and after surgery, to standard-of-care treatment for high-risk, early-stage TNBC. Based on biological and clinical rationale, administration of immunotherapy, both pre- and post-operatively, may provide the highest therapeutic benefit in the curative setting.

The single-study approach includes both neoadjuvant phase, which ends after definitive surgery, and an adjuvant phase, which starts from the first adjuvant treatment and includes radiation therapy as indicated.

KEYNOTE-522 enrolled patients with centrally

confirmed TNBC who had either T1c N1 to 2 disease or T2 to 4 tumors independent of nodal involvement. All patients had stage 2 or stage 3 disease. Patients were randomized 2 to 1 to pembrolizumab plus neoadjuvant carboplatin plus paclitaxel, followed by doxorubicin or epirubicin plus cyclophosphamide with pembrolizumab given throughout or to placebo, plus the same chemotherapy regimen.

Certification factors included nodal status positive versus negative; tumor size, T1/2 versus T3/4; and carboplatin scheduled weekly versus every 3 weeks. After surgery, patients in the pembro group continued with adjuvant pembrolizumab for a total of one year of pembrolizumab exposure, whereas patients in the control group received placebo.

The dual primary endpoints included pathological complete response defined as ypT0/Tis ypN0 assessed by the blinded local pathologist and event-free survival assessed by the investigator. The sample size was driven by EFS.

The total alpha was 2.5 percent one-sided placed between the dual primary endpoints. An initial alpha of 0.5 percent was allocated to the path CR endpoint and 2 percent was allocated to EFS. If path CR was statistically significant, the alpha would be transferred to EFS.

Interim analysis 1 in September 2018 was triggered by completion of enrollment and included the first 602 randomized patients who had, or should have completed, surgery by that time. It was the first analysis for path CR and was the prespecified primary path CR analysis.

Interim analysis 2 in April 2019 occurred 24 months after the first patient was randomized. This was the final analysis of path CR, and it was based on the first 1,002 randomized patients per protocol. IA2 was also the first interim analysis of EFS based on all 1174 patients randomized, the intention-to-treat population.

Interim analysis 3 occurred in March 2020 and included approximately 53 percent of EFS events required for the final analysis. We will present

path CR rates at each interim analysis, and for EFS, we will focus on interim analysis 3 with the longest follow-up.

Subsequent interim analysis for EFS are planned until the final analysis at 327 events, which is expected to occur in 2025. Overall survival will only be tested if the EFS endpoint is met. We will show you the analysis of OS at interim analysis 3.

Baseline characteristics were well balanced between treatment groups. The median age was 48 to 49 years. Over 80 percent of patients had PD-L1 positive tumors at the CPS cutoff of 1, and more patients received weekly carboplatin. In 74 percent of patients, tumor size was T1 or T2, and about half the patients had nodal involvement. About one-quarter of patients had stage 3 disease at study entry.

Baseline demographics in terms of race and geographic region were also well balanced between treatment groups. About 50 percent of patients were enrolled in Europe, 20 percent in North

America, and 20 percent in Asia. A total of 1174 patients were randomized 2 to 1 from March 2017 to September 2018, and they make up the intention-to-treat population EFS.

Seven randomized patients did not start neoadjuvant therapy. About 98 percent of patients in both treatment groups had documented surgery, and 75 percent of patients in the pembro group and 85 percent in the control group started adjuvant treatment.

Per protocol, patients who discontinued pembrolizumab or placebo due to adverse events during the neoadjuvant phase were not allowed to receive pembro or placebo after surgery. The median follow-up in both treatment groups was approximately 26 months at interim analysis 3.

The analysis of path CR of interim analysis 1 is shown here. This was the primary path CR analysis for the study. Pembrolizumab met the primary path CR endpoint with a path CR rate of 64.8 percent in the pembro group compared with 51.2 percent in the control group.

The estimated delta based on a stratified model was 13.6 percent with a p-value of 0.00055. This was a statistically significant improvement in the path CR rate, and the absolute path CR rate achieved with pembrolizumab is the highest reported in a randomized study in this patient population.

Of note, the observed path CR benefit was independent of PD-L1 status at the prespecified CPS threshold of 1. The estimated delta in the stratified model was 14.2 percent for the CPS at-least-1 population and 18.3 percent for the CPS less-than-1 population.

Here is the prespecified subgroup analysis for path CR at interim analysis 1. Pembrolizumab plus chemotherapy consistently increased the path CR rate compared with placebo plus chemotherapy across subgroups consistent with the primary path CR analysis.

Of note, the path CR improvement in node-positive patients, representing about half of patients enrolled, was 21 percent. At interim analysis 2, based on the first 1,002 patients, the

path CR rate was 64 percent in the pembro group and 54.7 percent in the control group, and the delta remained statistically significant. This result is supportive of the primary path CR analysis at interim analysis 1. At interim analysis 3, a descriptive path CR analysis based on all 1174 patients showed a path CR rate of 63 percent in the pembro group and 55.6 percent in the control group.

Here is the first EFS analysis at interim analysis 2 performed 24 months after the first patient was randomized at the median follow-up of 15.5 months. The hazard ratio was 0.63. And here is the first analysis at interim analysis 3, which was performed 36 months after the first patient was randomized at the median follow-up of 26 months.

The minimum follow-up for IA3 was about 18 months, so the EFS data up to that point will not change. Pembrolizumab administered pre- and post-operatively resulted in a 35 percent reduction in the risk of disease progression, recurrence, or death. The hazard ratio was 0.65.

At 27 months, the EFS rates were 86.6 percent in the pembro group compared to 79.4 percent in the control group. At interim analysis 3, the p-value for EFS was 0.0025, which did not cross the precalculated boundary for significance of 0.0021.

We recognize that there is interest in understanding the probability of success for EFS, and as you saw in the briefing document, FDA calculated the predictive power for interim analysis 4 at 62 to 78 percent. We calculated the Bayesian predictive power of achieving a significantly EFS result at the next interim analysis and for the remainder of the trial, based on the observed data at interim analysis 3.

Based on our model assumptions, we calculated a 73 percent probability for statistical significance at interim analysis 4 within the FDA's range of probabilities and greater than 95 percent for the remainder of the trial. When we applied FDA's methodology, we were able to replicate their estimate of predictive probability at interim

analysis 4, and when we applied that methodology to the remainder of the trial, the outcome was consistent with our analysis. Dr. Berry is with us to answer any questions about the model.

Now we look at EFS by treatment group and whether patients had a path CR or not of definitive surgery. It is important to keep in mind that this is not a randomized comparison within each subgroup, path CR yes or no.

On the far right, you can see the percentage of patients within each treatment group who are represented in each of the respective curves. Patients who achieved a path CR had a more favorable long-term outcome, and the additional pembrolizumab to neoadjuvant chemotherapy increased the number of patients in this category.

Notably, the curves separated at about 20 months, and the 27-month EFS rates were 96.6 percent in the pembro group and 93.5 percent in the control group. Patients who did not achieve a path CR had an overall worst outcome as expected, but the curves separated again in favor of the

pembro group, this time at an earlier time point at about 15 months. The 27-month EFS rates were 69.5 percent in the pembro group and 61.7 percent in the control group.

In the prespecified subgroup analysis, EFS consistently favored the pembrolizumab regimen over control at interim analysis 3. Here is the overall survival at interim analysis 3 with a median follow-up of 26 months. At this early time point, approximately 32 percent of required events have been observed. Since EFS did not reach statistical significance, no hypothesis testing was performed for OS. The hazard ratio was 0.80.

Now turning to safety, the following slides represent the safety data from interim analysis 3 because that is the longest follow-up. The pembrolizumab safety profile is well characterized based on an extensive clinical trial program and postmarketing experience. We reviewed the safety data from KEYNOTE-522 in the context of the pembrolizumab reference safety data set, or RSD, which is composed of 2799 patients with advanced

melanoma and non-small cell lung cancer. It represents the established safety profile of pembrolizumab monotherapy.

Safety was evaluated in all patients who received at least one dose of study treatment or surgery. The median duration of exposure was about 5 months in both neoadjuvant and adjuvant phases, and it was consistent between treatment groups.

This is a high-level summary of the safety profile in the neoadjuvant and adjuvant phases separately. In the neoadjuvant phase, the overall rate of adverse events in grade 3 to 5 adverse events were generally balanced across treatment groups. There were more serious adverse events and adverse events leading to discontinuation in the pembro group, reflecting the incremental toxicity of adding pembrolizumab to chemotherapy; however, no new safety concerns were identified.

In the adjuvant phase, patients experienced fewer adverse events overall and fewer grade 3 to 5 adverse events, serious adverse events, discontinuations due to adverse events, and

immune-mediated adverse events compared to the neoadjuvant phase. In the neoadjuvant phase, there were 5 deaths in the pembro group and 1 death in the control group due to adverse events with an incidence of 0.6 percent versus 0.3 percent. In the adjuvant phase, there were 2 deaths in the pembro group. In total, 3 deaths due to pneumonitis, pulmonary embolism, and autoimmune encephalitis were considered by the investigator to be related to pembrolizumab.

The most common grade 3 to 5 adverse events were overall balanced between treatment groups. During the neoadjuvant phase, these were primarily chemotherapy-related hematologic toxicities; therefore, adding pembrolizumab to chemotherapy did not increase the severity of common chemotherapy-related adverse events. During the adjuvant phase, the incidence was much lower, and individual events were observed in less than 1 percent of patients.

As mentioned, serious adverse events occurred at a higher frequency in the pembro group compared to the control group. During the

neoadjuvant phase, pyrexia, adrenal insufficiency, and the AEs, or adverse events, occurring in less than 1 percent of patients accounted for much of the increase in serious adverse events observed in the pembro group. Again, there was no pattern suggesting a new safety concern. The incidence of serious adverse events was low during the adjuvant phase.

Immune-mediated adverse events and infusion reactions were higher in the pembro group compared to the control group and the RSD. Most events were low grade and non-serious. There were 2 deaths due to an immune-mediated adverse event in the pembro group, an event of pneumonitis during the neoadjuvant phase, and an event of autoimmune encephalitis during the adjuvant phase.

The high-end frequency of immune-mediated adverse events in the pembro group was primarily driven by infusion reactions, hypothyroidism, and severe skin reactions occurring during the neoadjuvant phase. Infusion reactions and severe skin reactions reflected the contribution of both

pembrolizumab and chemotherapy.

The types, nature, and severity of immune-mediated adverse events observed in the pembro group were generally consistent with the RSD, and no new indication specific immune-mediated adverse events causally related to pembro were identified.

Taking all this data into consideration, we would like to offer the following conclusions. Based on a strong biological and clinical rationale, the KEYNOTE-522 regimen, with one year of add-on pembrolizumab, given before and after surgery, was designed to provide patients with high-risk, early-stage TNBC with the highest possible benefit from the use of immunotherapy in the curative setting. Given this design, the relative contributions of neoadjuvant and adjuvant pembrolizumab to the EFS benefit cannot be deciphered.

KEYNOTE-522 demonstrated a statistically significant path CR improvement compared with platinum-based chemotherapy and the highest absolute path CR rate ever reported in TNBC. This

is very important at the individual patient level. The KEYNOTE-522 regimen also showed a promising and stable effect on EFS at interim analysis 3 with a hazard ratio of 0.65.

This EFS improvement exceeds what would have been predictive from a modest path CR improvement in the intention-to-treat population as modeled from earlier neoadjuvant chemotherapy trials. Importantly, although the EFS did not reach statistical significance at interim analysis 3, the predictive probability of success for the entire study is high.

The safety profile was consistent with the individual profiles of pembrolizumab and platinum-based chemotherapy and adverse events were manageable with standard measures. No new safety concerns were identified. The role of pembrolizumab in the treatment of TNBC is further supported by significant PFS benefit observed in the metastatic setting.

Therefore, given the favorable benefit-risk profile of the KEYNOTE-522 regimen and the unmet

medical need in this high-risk patient population, where [indiscernible] recurrence have a very poor prognosis, we are seeking accelerated approval to bring this regimen to patients.

Thank you for your attention, and now Dr. Rugo will provide her clinical perspective.

Applicant Presentation – Hope Rugo

DR. RUGO: Thank you, Dr. Karantza.

I'm Hope Rugo from the University of California San Francisco Comprehensive Cancer Center. I'm going to provide a brief clinical perspective on the data that you've just heard in the context of what Dr. O'Shaughnessy presented a little earlier. I am an investigator in KEYNOTE-355 and other Merck-sponsored and investigator-initiated trials of pembrolizumab. I am not receiving compensation for my presentation today and have no financial interest in the outcome of this meeting.

KEYNOTE-522 has established a new treatment paradigm in TNBC based on a strong biologic rationale for the addition of immunotherapy to

neoadjuvant chemotherapy while the primary tumor is still present. Adjuvant administration of immunotherapy may further enhance anti-tumor immunity and has been shown to prolong disease-free survival in multiple other tumor types.

In early-stage HER2-positive breast cancer, there is precedent for the use of trastuzumab, a drug with known immunomodulatory properties for one year, including both the pre- and post-operative setting, independent of achieving path CR at definitive surgery.

The risk of disease recurrence in early-stage TNBC is highest in the first 1 to 3 years following diagnosis; therefore, it is critical to provide the most effective therapy as early as possible in the curative setting, where we know that achieving a path CR for an individual patient has a significant and meaningful impact on survival.

A number of neoadjuvant studies with immunotherapy have reported interesting findings that support the role for immunotherapy in TNBC.

As you can see, KEYNOTE-522 is the largest study to report results to date and reported the highest path CR rate with a statistically significant improvement compared with chemotherapy.

The fact that the path CR rate was improved regardless of PD-L1 expression suggests that PD-L1 is not a predictive marker for the impact of immunotherapy on path CR when the immune system is intact, but data across PD-L1 status suggest that this marker may be predictive for chemotherapy benefit in early-stage TNBC. It is also noteworthy that the path CR rate in the control arm was quite high due to the use of carboplatin.

The phase 2 I-SPY2 trial showed an improvement in the estimated path CR rate when patients received only 4 doses of pembrolizumab with paclitaxel followed by AC, compared with standard taxane anthracycline chemotherapy. IMpassion 031, with just over 300 randomized patients, showed that the addition of atezolizumab to nab-paclitaxel, followed by anthracycline-based chemotherapy, significantly improved the path CR

rate regardless of PD-L1 status, similar to KEYNOTE-522.

Of note, two trials, NEOTRIP and GEPARNUEVO, did not show a significant benefit in path CR with the addition of checkpoint inhibitors to standard chemotherapy. NEOTRIP used a taxane and platinum chemotherapy regimen, suggesting that anthracyclines may be important to obtain the greatest benefit from immunotherapy as measured by path CR.

GEPARNUEVO enrolled a high proportion of patients with very early-stage node-negative disease and incorporated the checkpoint inhibitor, durvalumab. This raises the possibility that the trial was underpowered for those who might benefit the most from immunotherapy, those with higher stage node-positive disease.

The magnitude of path CR improvement needed to achieve a meaningful EFS improvement in a single study is not known. However, multiple studies, including the Cortazar meta-analysis CALGB 40603 and I-SPY2, have shown strong patient-level

association between path CR and event-free survival in TNBC . Patients who achieve a path CR have significantly improved long-term outcomes. Results from KEYNOTE-522 show a consistent patient-level association between path CR and event-free survival in both the pembro and placebo arms.

Based on the data from KEYNOTE-522, it appears that the benefit of immunotherapy in TNBC goes beyond what is captured by the improvement in path CR. This may be due to the mechanism of action of immunotherapy and/or adjuvant exposure to pembrolizumab.

Data from immunotherapy studies in various metastatic indications have shown that the modest improvements in response can be associated with meaningful survival benefit. Given this observation, it is likely that a modest improvement in path CR could be associated with a significant event-free survival benefit.

The figure on the left shows the KEYNOTE-522 IA3 event-free survival data superimposed on that of CALGB 40603, which accrued patients between 2009

and 2012. Although CALGB 40603 was a small 4-arm study, it does provide some indication about the event rate over time for patients with TNBC treated with neoadjuvant chemotherapy. Most event-free survival events in early-stage TNBC occur within the first three years, followed by a relative plateau.

Given the strong predictive probability that event-free survival benefit will be demonstrated in KEYNOTE-522 when the data matures, the totality of the evidence supports the spirit of accelerated approval of pembrolizumab plus chemotherapy in the setting of a pressing unmet need for patients with high-risk, early-stage TNBC.

With regards to safety, I think it's encouraging to see that, overall, adverse events were consistent with the individual safety profiles of pembrolizumab and platinum-based chemotherapy. The addition of pembrolizumab to chemotherapy did not increase the incidence or severity of common chemotherapy-related toxicities.

Most immune-related adverse events occurred

during the neoadjuvant phase. Monitoring for an early identification of immune AES is critical. For example, we routinely monitor for thyroid abnormalities. It's interesting that some of the patients on the placebo arm have thyroid abnormalities, highlighting that this is a common endocrine finding. There was an increase in severe skin reactions, which generally can be controlled with steroids, and patients may be able to be safely retreated with immunotherapy.

A brief mention about adrenal insufficiency and hypophysitis, these toxicities are seen across many different immunotherapy agents in patients with breast cancer. Understanding how to identify this toxicity allows effective management with hydrocortisone while continuing therapy.

Overall, no new safety concerns were identified for the use of pembrolizumab plus neoadjuvant chemotherapy as neoadjuvant treatment followed by pembrolizumab monotherapy and as adjuvant treatment of high-risk, early-stage TNBC.

Now let me briefly mention the data from

KEYNOTE-355.

Can you hear me?

(No response.)

DR. RUGO: Now let me briefly mention the data from KEYNOTE-355 that also supports the role of immunotherapy in TNBC. KEYNOTE-355 is an ongoing, randomized, phase 3 study for metastatic TNBC not previously treated with chemotherapy, and it demonstrated a statistically significant and clinically meaningful improvement in PFS.

These results were the basis for accelerated approval of pembrolizumab in the treatment of metastatic TNBC with a CPS of 10 or greater. Early-stage TNBC is immunologically distinct from metastatic TNBC, which may explain why benefits in pCR and EFS are seen regardless of PD-L1 positivity in KEYNOTE-522.

Today you will be asked to consider whether we should wait for more data from KEYNOTE-522 to approve this regimen. I would like to tell you why I think we should not wait to make the KEYNOTE-522 regimen available to patients with high-risk,

early-stage TNBC.

Looking at the number of new cases of early-stage TNBC that are diagnosed annually in the United States and modeling of available data from CALGB 40603 and KEYNOTE-522 at IA3, we can estimate that we would need to treat 17 to 25 patients with pembrolizumab added to standard-of-care chemotherapy to prevent one event-free survival event.

Therefore, waiting for the EFS data to mature could mean that approximately 4 to 6 percent, or 7[000] to 10,000, more U.S. patients could have a recurrence of TNBC over five years. This is particularly important, given that patients with recurrent distant metastatic TNBC have a median overall survival of only 18 to 24 months.

With these data, how would I use pembrolizumab in clinical practice? I think pembrolizumab, in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab monotherapy, represents a new standard of care for

patients who have early-stage TNBC with high-risk clinical pathologic features, including stage 2 or 3 disease and lymph node involvement.

This group of patients have a high unmet need with limited treatment options. Immune-mediated adverse events can be successfully managed in clinical practice. Increasing provider and patient awareness through labeling and a medication guide will enable early recognition and intervention to minimize risk and enhance the potential for benefit to patients.

Thank you for your attention, and now I will turn it over to Dr. Goodman from Merck, who will moderate the QA.

DR. GOODMAN: Thank you, Dr. Rugo.

DR. CHEN: Actually --

DR. HOFFMAN: Actually, we're not ready for the QA yet, I believe.

DR. CHEN: Yes. Thank you.

DR. GOODMAN: Understood. Can I just introduce myself quickly, and then go to the FDA presentation? Would that be ok?

DR. HOFFMAN: Yes.

DR. CHEN: Go ahead.

DR. GOODMAN: So I'm Dr. Vicki Goodman, vice president of clinical research and therapeutic area head of late-stage oncology at Merck. This concludes the sponsor presentation, and we'll look forward to addressing your questions after the FDA presentation.

DR. HOFFMAN: Thank you.

We will now proceed with the FDA presentation.

FDA Presentation – Mirat Shah

DR. SHAH: Good morning. My name is Mirat Shah, and I'm a medical oncologist who is the clinical reviewer for this supplemental biologic license application for pembrolizumab. This application was submitted by Merck, who I will refer to as the applicant for the rest of the presentation.

This slide shows the members of the multidisciplinary FDA review team for this pembrolizumab supplemental application, and my

presentation reflects their collective input. The applicant has proposed the following indication. Pembrolizumab is indicated for the treatment of patients with high-risk, early-stage, triple-negative breast cancer in combination with chemotherapy of neoadjuvant treatments, and then as a single agent for adjuvant treatment following surgery.

The applicant is seeking an accelerated approval of the entire regimen based on demonstration of improvement and pathologic complete response, pCR rates, and an event-free survival, or EFS result, which is immature. For an accelerated approval, continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

To support this indication, the applicant submitted results from the KEYNOTE-522 study. In this study, patients are randomized 2 to 1 to receive either pembrolizumab or placebo in combination with chemotherapy as neoadjuvant treatments, and then as monotherapy for adjuvant

treatment following surgery.

This type of trial design is called an add-on design because experimental treatment, in this case neoadjuvant and adjuvant pembrolizumab, is added to standard treatment, and this is compared to standard treatment alone. The co-primary endpoints were pCR rate and EFS, and overall survival, or OS, was a key secondary endpoint.

As a reminder, pCR rate was defined as the proportion of patients without invasive residual cancer in breast or lymph nodes at time of surgery. EFS was defined as time from randomization to either progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. As pCR rate is measured at the time of surgery, it only captures the effect of the neoadjuvant portion of treatment, not the adjuvant portion. In contrast, EFS and OS measure the effect of neoadjuvant and adjuvant treatment.

These are the main KEYNOTE-522 study

results. At interim analysis 3 when all randomized patients were included in the pCR analysis, the difference in pCR rate between treatment arms was 7.5 percent with a 95 percent confidence interval of 1.6 percent to 13.4 percent.

EFS and OS data were immature. Additionally, pembrolizumab was associated with increased immune-mediated adverse events, or AEs, and the FDA considers 4 deaths as potentially due to immune-mediated AEs.

These are the key issues with the application. The key efficacy issues include that neoadjuvant pembrolizumab confers only as small absolute improvement in pCR rate, which has questionable clinical meaningfulness. EFS and OS data are immature and unreliable. The current trial results do not support a role for adjuvant pembrolizumab. And finally, supportive evidence of clinical benefit from another treatment setting is lacking. The key safety issue is that the pembrolizumab regimen is associated with increased toxicity from immune-mediated AEs.

The FDA would like to highlight some portions of the regulatory history of this application. The FDA met with the applicant in December 2018 and discouraged application submission based on pCR results at interim analysis 1, as the pCR rate difference between treatment arms was small and had uncertain clinical meaningfulness.

The FDA met with the applicant in September 2019 and again discouraged submission, as pCR rate difference was small and EFS results were immature at interim analysis 2, leading to uncertainty regarding benefit. On May 8, 2020, the applicant's external data monitoring committee met and recommended continuing the trial without change, as the EFS endpoint was not met at interim analysis 3, however, on May 29, 2020, the pembrolizumab application was submitted.

This is the outline of the presentation. I will go through the key efficacy issues and key safety issue of the application, summarize our conclusions, and finish with the ODAC voting

question.

I will start with the key efficacy issues. The first efficacy issue is that there is a small absolute improvement in pCR rate which is of questionable clinical meaningfulness. Before I discuss the pCR results from KEYNOTE-522, I will provide some context for how the FDA evaluates a pCR endpoint in breast cancer.

The FDA published a guidance on the use of the pCR endpoint to support an accelerated approval for neoadjuvant treatment of high-risk, early-stage breast cancer. A large difference in pCR rate between treatment arms of a clinical trial may be reasonably likely to predict clinical benefit; however, using a pCR endpoint is challenging, as there is uncertainty about its relationship to clinical benefit. I will summarize some of the information included in the guidance on the next two slides.

The FDA convened an international working group to assess the association between pCR and EFS and OS in a pooled analysis. EFS and OS are

established endpoints of clinical benefit. The analysis found that at the patient level, individual patients experiencing a pCR, regardless of treatment received, had an improvement in EFS and OS compared to patients with residual disease at time of surgery. However, at the clinical trial level, an improvement in pCR rates in the experimental arm did not necessarily translate to an improvement in EFS or OS over the control arm.

Some trials that have shown a difference in pCR rates between treatment arms have failed to show a difference between arms in long-term outcomes. Therefore, pCR rate is not an established surrogate for EFS or OS at the clinical trial level and cannot be viewed as an established measure of clinical benefit.

If pursuing approval based on a pCR endpoint, there are two trial design options, the single-trial model and the multiple-trial model. In the single-trial model, one neoadjuvant study is powered to detect an improvement in pCR rate and in EFS. The pCR results are available first, and if

sufficiently compelling may support an accelerated approval. The EFS results are available later and used to convert this to a regular approval.

Importantly, since this type of trial is powered based on EFS, it may be overpowered for pCR, which means that it may be able to detect a statistically significant difference in pCR rate that is too small to be clinically meaningful.

In the multiple-trial model, the initial neoadjuvant study is powered to detect a substantial improvement in pCR rate and potentially support an accelerated approval. The subsequent study to convert to regular approval can take place in either the neoadjuvant or adjuvant setting and is powered to detect either an improvement in EFS or in disease-free survival, or DFS, for an adjuvant study. KEYNOTE-522 followed the single-trial model by assessing pCR rate and EFS in the same trial.

In determining whether to grant accelerated approval for neoadjuvant treatment based on a pCR endpoint, the FDA considers the magnitude of

improvement in pCR rate and the acceptability of the added toxicity in a group of patients with potentially curable disease.

Additionally, compelling data of clinical benefit from another treatment setting may help mitigate some of the uncertainty associated with the pCR endpoint.

To date, only one treatment, pertuzumab, has received accelerated approval based on a pCR endpoint. Pertuzumab is a HER2-targeted monoclonal antibody indicated for neoadjuvant treatment of patients with HER2-positive breast cancer. This approval was based on an overall positive benefit-risk assessment, which included data showing overall survival benefit from the metastatic setting.

With that background on the pCR endpoint, I will now discuss the results from KEYNOTE-522. The co-primary endpoint, the pCR rate, measures the impact of neoadjuvant treatment only. In a randomized trial, we evaluate the benefit of pembrolizumab in the context of the control arm by

using the difference in pCR rate between the two arms rather than assessing the pembrolizumab arm alone.

This plot shows the pCR rate on the pembrolizumab and chemotherapy arm in a blue bar and the pCR rate on the placebo and chemotherapy arm in a red bar at interim analysis 1, 2, and 3. The pCR rate difference between the two arms is shown above the bars at each time point, and this difference gets smaller as more patients are added to the analysis population.

We agree with the applicant that a statistically significant difference in pCR rate was observed at interim analysis 1, however, at this time point, only approximately half of patients randomized were included in the pCR analysis.

We instead consider the clinical meaningfulness of the pCR rate difference based on interim analysis 3 because this time point includes all 1174 patients who were randomized and is therefore a more appropriate estimate of pCR rate

for a population of patients with triple-negative breast cancer.

At interim analysis 3, although a high pCR rate of 63 percent was observed for the pembrolizumab arm, the pCR rate for the control arm was 56 percent. Therefore, based on all patients included in KEYNOTE-522, the difference between arms is only 7.5 percent with a 95 percent confidence interval of 1.6 percent to 13.4 percent. There is uncertainty regarding whether the small pCR rate difference is clinically meaningful and will translate to a true clinical benefit based on EFS or OS.

The second efficacy issue is that EFS and OS data are immature and unreliable. The co-primary endpoint, EFS, incorporates the effect of neoadjuvant and adjuvant treatment. At interim analysis 3, EFS did not cross the prespecified efficacy boundary, and the applicant's data monitoring committee recommended continuing the study without change. EFS data remain immature at interim analysis 3 and only 53 percent of the EFS

events needed for the final analysis have occurred.

The FDA notes that interim analyses may overestimate the treatment effect, particularly when the number of events is small. Although the p-value is small, it has not crossed the prespecified statistical boundary and does not predict whether EFS will be statistically significant at a later time point. There is still a great deal of uncertainty associated with the EFS estimate.

I want to further consider the EFS results at IA3 and take a moment to explain why adherence to the prespecified statistical plan is needed and why a trial should not be declared successful early, based on a p-value that appears close to the boundary at one interim analysis.

In general, there should be a prospective plan to maintain type 1 error control or control of false positive findings. The overall one-sided alpha of 0.025 needs to be split to account for analyses of multiple endpoints like pCR and EFS and also to account for multiple interim analyses of

the same endpoint.

For EFS, six interim analyses and one final analysis are planned. The alpha allocated to each EFS analysis is based on the actual number of events that have occurred. If only a few events have occurred in early looks, the alpha allocated to the analysis will be smaller.

For these statistical methods to be valid, it is important to adhere to the prospective analytic plan and declare trial success at an interim look only if the statistical criteria are met; otherwise, there is a risk of declaring success based on false positive findings.

A p-value that appears close to the allocated alpha at one time point does not predict what will happen at future time points. The statistical boundary for EFS was not crossed at IA3, and the applicant's data monitoring committee recommended continuing the study without change.

The FDA and the applicant both examined the predictive probability of EFS reaching statistical significance in a future analysis. As seen on this

slide, the predicted probability of EFS achieving statistical significance at the next interim analysis, which is IA4, is highly variable, ranging from 62 to 78 percent in the FDA's model and 32 to 92 percent based on the applicant's model.

Predictive probability models are highly sensitive to modeling assumptions and become even less reliable after interim analysis 4 due to little available information. For this reason, the FDA did not predict probability of success at future analyses after IA4. This type of model is not a reliable way to assess the effect of neoadjuvant and adjuvant pembrolizumab on EFS, and -- [inaudible – audio gap].

DR. SHAH: This is Mirat. My audio was disconnected, and I will start at the top of this slide if that's acceptable.

CAPT WAPLES: Yes. Yes, it is.

DR. SHAH: Okay. Thank you.

So starting with the predictive probability of EFS effect, slide 19, the FDA and the applicant both examined the predicted probability of EFS

reaching statistical significance in a future analysis. As seen on the slide, the predicted probability of EFS achieving statistical significance at the next interim analysis, which is IA4, is highly variable, ranging from 62 to 78 percent in the FDA's model and 32 to 92 percent based on the applicant's model.

Predictive probability models are highly sensitive to modeling assumptions and become even less reliable after interim analysis 4 due to little available information. For this reason, the FDA did not predict probability of success at future analyses after IA4.

This type of model is not a reliable way to assess the effect of neoadjuvant and adjuvant pembrolizumab on EFS and cannot replace the continued follow-up which is needed for patients enrolled to KEYNOTE-522. The next interim analysis, IA4, will take place in summer of 2021.

One additional note, the FDA's regulatory decisions are not only based on statistical significance of an efficacy endpoint but also the

reliability of the interim result, clinical relevance of the result, and the adequacy of data with regards to other issues such as overall survival and safety.

This plot shows EFS in patients by pCR status and treatment assignment. The top two curves represent patients who experience the pCR and the bottom two curves represent patients who have residual disease at time of surgery. This type of analysis is called a responder analysis, is exploratory, and cannot be used to justify that patients who received pembrolizumab benefited regardless of initial response to neoadjuvant treatment.

Randomization is not preserved, so differences between pCR and no-pCR population, and between treatment arms within these populations, may be due to differences in measured and unmeasured baseline prognostic factors. Additionally, the number of events is small and the shaded portions of the graph representing the 95 percent confidence band are widely overlapping.

This indicates that there is a high level of uncertainty regarding improvement in EFS in the pembrolizumab arm for either the pCR or no-pCR populations.

Next, I will review the key secondary endpoint overall survival, which like EFS incorporates the effect of neoadjuvant and adjuvant treatment. As EFS did not meet its prespecified threshold at IA3, OS was not formally tested. Additionally, only 32 percent of events needed for the final analysis have occurred. As OS data are immature, the OS hazard ratio estimate is unreliable.

The third efficacy issue is that the current KEYNOTE-522 trial results do not support a role for adjuvant pembrolizumab. As a reminder, this is the KEYNOTE-522 trial design. The applicant is seeking approval for neoadjuvant and adjuvant pembrolizumab. pCR endpoint measures neoadjuvant treatment effect only, whereas the EFS and OS endpoints incorporate the effect of the entire treatment regimen.

One uncertainty built into this trial design is that all patients randomized to the experimental arm are planned to receive neoadjuvant and adjuvant pembrolizumab. Therefore, it is not possible to determine the relative contribution of the neoadjuvant and adjuvant portions of treatment on an observed EFS or OS result.

Even if an improvement in EFS or OS is seen, it would not be possible to determine whether both portions of treatment were needed. Currently, as the EFS and OS data are immature, justification for the entire KEYNOTE-522 regimen, which includes adjuvant treatment with pembrolizumab, is lacking.

The final efficacy issue is that supportive data of clinical benefit from another treatment setting are lacking. Earlier in the presentation, I mentioned that pertuzumab for HER2-positive breast cancer is the only product to receive accelerated approval based on a pCR endpoint, and in that benefit-risk assessment, the FDA had relied on metastatic data. At the time of its neoadjuvant approval, pertuzumab had demonstrated unequivocal

benefit in the metastatic setting with at least a 10-month median overall survival improvement.

In contrast, these are the data for pembrolizumab from the metastatic triple-negative breast cancer setting. KEYNOTE-119 compared pembrolizumab monotherapy to physician's choice chemotherapy. The primary endpoint was overall survival in different tumor PD-L1 combined positive-score populations.

Combined positive score, or CPS, is a measurement of tumor PD-L1 status. To assign a CPS, the number of PD-L1 staining cells, including tumor cells, lymphocytes and macrophages, is divided by the total number of viable tumor cells and then multiplied by 100. A higher CPS indicates a higher proportion of cells that express PD-L1.

In KEYNOTE-119, OS improvement was not demonstrated in the PD-L1 CPS 10 or greater or 1 or greater populations. Because the OS endpoint was not met in these populations, it could not be tested in all patients unselected by tumor PD-L1 status.

In KEYNOTE-355, pembrolizumab in combination with physician's choice chemotherapy was compared to placebo and physician's choice chemotherapy. The initial primary endpoint was progression-free survival, or PFS, in all patients unselected by tumor PD-L1 status and PFS in those with tumor PD-L1 CPS 1, or greater.

Following an interim analysis where the primary endpoint did not cross the prespecified efficacy boundary, and based on emerging data from external studies, the protocol was amended to assess PFS in patients with tumor PD-L1 CPS 10 or greater. The PFS endpoint was only met in this subgroup due to -- [inaudible – audio gap].

There was uncertainty regarding clinical benefit even in this subgroup due to the timing of the late amendment and because PFS benefit was modest and OS benefit had not been demonstrated. Accelerated approval was granted for patients with tumor PD-L1 CPS 10 or greater, and clinical benefit needs to be confirmed.

In summary, for pembrolizumab, there is

uncertainty regarding clinical benefit in the metastatic setting. Potential benefit is restricted to patients with tumor PD-L1 CPS 10 or greater, and OS benefit has not been demonstrated.

Now I will return to data and results for pembrolizumab from KEYNOTE-522. Because data in the metastatic triple-negative breast cancer setting showed increasing pembrolizumab treatment effect with increasing tumor PD-L1 CPS, the FDA conducted a post hoc exploratory subgroup analysis to examine the relationship between pembrolizumab and tumor PD-L1 in the early-stage setting in KEYNOTE-522. This type of post hoc exploratory subgroup analysis must be interpreted with caution.

With this caveat, the pembrolizumab treatment effect on pCR rate was modest regardless of tumor PD-L1 status, including in those with tumor PD-L1 CPS 10 or greater. These results suggest that there is uncertainty regarding the role of tumor PD-L1 in predicting response to pembrolizumab in the early setting compared to the metastatic setting.

The efficacy conclusions are as follows. It is unclear if current efficacy results are reasonably likely to predict clinical benefits for neoadjuvant and adjuvant pembrolizumab for high-risk, early-stage, triple-negative breast cancer.

The pCR endpoint measured neoadjuvant treatment effect only, and there was a small absolute improvement in pCR rate, which further decreased as more patients were added to the analysis population. This pCR rate difference has questionable clinical meaningfulness.

The EFS and OS endpoints incorporate the entire neoadjuvant and adjuvant treatment regimen and are the only endpoints which can support the adjuvant portion. EFS and OS data are immature and unreliable, and therefore data are lacking to support the entire neoadjuvant and adjuvant pembrolizumab regimen.

Finally, data from the metastatic setting are not supportive of clinical benefit in the early-stage setting. Continued follow-up of

patients on KEYNOTE-522 for long-term outcomes is necessary to characterize whether there is clinical benefit of neoadjuvant and adjuvant pembrolizumab for high-risk, early-stage, triple-negative breast cancer.

I will now review the key safety issues for this application. Pembrolizumab is associated with increased immune-mediated toxicity. The FDA notes that many patients with high-risk, early-stage, triple-negative breast cancer will be cured with standard therapy, and therefore the added toxicity of pembrolizumab, and particularly side effects that may be severe, irreversible, or require lifelong medication, must be carefully considered.

Due to its mechanism of action and based on prior experience, pembrolizumab may be associated with a range of immune-mediated adverse events, or AEs, as well as infusion reactions. Combining the neoadjuvant and adjuvant phases, 43 percent of patients who received pembrolizumab experienced an immune-mediated AE or infusion reaction of any grade, including 15 percent of patients with an

event that was grade 3 or greater and 10 percent of patients who experienced an event requiring hospitalization. Dose modification due to immune-mediated AEs or infusion reactions was also more common with pembrolizumab compared to placebo.

Again, combining the neoadjuvant and adjuvant phases, the specific immune-mediated AEs experienced by patients who received pembrolizumab or placebo are shown in this table. The events experienced most frequently by patients who received pembrolizumab included infusion reaction, hypothyroidism, severe skin reactions, and hyperthyroidism.

Nineteen percent of patients who received pembrolizumab experienced an immune-mediated AE which was not resolved to baseline by last study assessment. Most immune-mediated AES that did not resolve were endocrine related. Eleven percent of patients who received pembrolizumab experienced unresolved hypothyroidism; 2 percent experienced unresolved adrenal insufficiency; and 2 percent experienced unresolved hypophysitis. Additionally,

16 percent of patients started thyroid hormone replacement while on study and 14 percent were still on replacement at last assessment.

The FDA disagrees with some of the applicant's patient death attributions. In patients who received pembrolizumab, there were 4 deaths which the FDA considers potentially due to immune-mediated AEs. These deaths were from adrenal crisis, pneumonitis, hepatitis, and autoimmune encephalitis.

One patient experienced adrenal crisis and died from shock on post-operative day 1 following her breast surgery. Her cortisol level was only 3 and she likely had undiagnosed adrenal insufficiency at the time of surgery. Although pembrolizumab is known to be associated with adrenal insufficiency, undiagnosed adrenal insufficiency caused by neoadjuvant treatment poses an increased risk in an early-stage breast cancer population where almost all patients will undergo surgery.

One patient died from autoimmune

encephalitis while receiving adjuvant pembrolizumab, highlighting that although most toxicity occurred during the neoadjuvant portion of treatment, the adjuvant portion of the treatment regimen may also come with risk.

Since EFS and OS data are immature, the adjuvant portion of pembrolizumab treatment has not demonstrated a significant effect on any efficacy endpoint, and the FDA looked closely at safety events during this treatment phase. Although there were fewer immune-mediated events than during the neoadjuvant phase, there was still a small increased risk of experiencing all grade immune-mediated AEs, higher grade immune-mediated AEs, or immune-mediated AEs leading to hospitalization.

The FDA also examined patient-reported outcomes, or PRO data, from KEYNOTE-522. Limitations of PRO data to characterize the experience of patients receiving pembrolizumab include that the PRO data are exploratory. There are no prespecified PRO hypotheses, and the PRO

endpoints were not statistically tested.

During the neoadjuvant and adjuvant period, PRO assessments are infrequent, and therefore insufficient to capture the symptoms, side effects, and functional impairments that could be associated with treatment. Because of the trial design, which did not include prespecified PRO hypotheses, one cannot conclude that there is no meaningful difference between arms in terms of quality of life, symptoms, and functioning. The FDA does not agree that PRO results support a positive benefit-risk assessment.

The safety summary is as follows. Pembrolizumab increased immune-mediated toxicities in a population where although patients are at increased risk of recurrence, many will be cured with standard therapy. Some of these immune-mediated toxicities, particularly endocrine-related toxicities, may be severe or irreversible, or require lifelong medication in patients cured of their breast cancer.

The adjuvant portion of the pembrolizumab

regimen added toxicity. Toxicities in the adjuvant phase are particularly concerning because EFS and OS data are immature, and this portion of the regimen has not demonstrated a significant effect on any efficacy endpoint and may be adding risk without benefit. Finally, PRO data are not supportive of a positive benefit-risk assessment.

I will now review our conclusions for this application. In summary, it is unclear if the current KEYNOTE-522 results support a favorable benefit-risk assessment for the neoadjuvant and adjuvant pembrolizumab regimen for patients with high-risk, early-stage, triple-negative breast cancer.

The pCR endpoint only reflects the neoadjuvant portion of treatment, and the improvement in pCR rate is small and of uncertain clinical meaningfulness. The EFS and OS endpoints reflect the entire treatment regimen. EFS and OS data are immature, so there is inadequate justification for the entire neoadjuvant and adjuvant regimen at this time.

Additionally, pembrolizumab adds immune-mediated toxicities, including some which may be severe, irreversible, or require lifelong medication in a population where many will be cured of their breast cancer. There are four additional interim analyses and a final analysis for EFS planned. An approval decision is premature at this time and further follow-up is needed.

The FDA will now present the voting question for the advisory committee. The voting question is, should a regulatory decision on pembrolizumab, in combination with multi-agent chemotherapy for neoadjuvant treatment, followed by pembrolizumab monotherapy for adjuvant treatment of high-risk, early-stage, triple-negative breast cancer, be deferred until further data are available from future analyses of KEYNOTE-522?

The FDA would like to know whether the committee thinks there is evidence of benefit to outweigh the risks of the pembrolizumab regimen at this time or whether we should await further data on long-term outcomes, including EFS and OS from

future analyses, before making a regulatory decision. Results from the next interim analysis will be available in summer of 2021. Thank you very much for your attention.

Clarifying Questions to Presenters

DR. HOFFMAN: We will now take clarifying questions for the presenters, both Merck Sharp & Dohme Corporation and the FDA. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

Dr. Armstrong?

(No response.)

DR. HOFFMAN: Unmute yourself and please go ahead.

DR. ARMSTRONG: Thank you. Can you hear me?

DR. HOFFMAN: Yes.

DR. ARMSTRONG: Thanks.

I had a couple of questions about the actual chemotherapy regimen, although Dr. O'Shaughnessy alluded to data supporting this. The regimen of carboplatin, paclitaxel, followed by anthracycline and cyclophosphamide, is not a standard chemotherapy regimen. For example, I don't believe that's listed in NCCN guidelines.

Could someone from the applicant address the rationale for that choice of the chemotherapy regimen?

DR. GOODMAN: This is Vicki Goodman, vice president of clinical research at Merck, and I will ask Dr. O'Shaughnessy if she'd like to comment on the chemotherapy regimen choice, please.

DR. O'SHAUGHNESSY: Yes. This is Joyce O'Shaughnessy, Baylor University Medical Center.

It's quite clear, as I showed you in my presentation, that you do improve the pathological complete response rate in triple-negative breast cancer with the addition of preoperative carboplatin to NACT regimen.

What has been less clear, and is still the subject of ongoing phase 3 prospective trials, is whether that translates into improved disease-free survival in large patient populations. There are smaller studies that suggest that that is the case, but we await the big phase 3 data.

Just this past weekend, the ASCO guidelines committee came out with a paper in JCO on neoadjuvant strategies for breast cancer in general, and in that paper they said that their opinion was that the addition of carboplatin to the preoperative ACT regimen was acceptable. So I think that kind of reflects what really is going on in practice these days.

DR. ARMSTRONG: Thank you, Joyce.

A second question was that the standard of care today for subjects with triple-negative breast

cancer who do not have a pathologic complete response is the use of capecitabine after surgery, and assuming that was not allowed, just to clarify that.

DR. GOODMAN: Vicki Goodman, vice president clinical research at Merck. The study was initiated and had enrolled a substantial number of patients, many of whom had reached the adjuvant phase prior to the release of the CREATE-X data on which that recommendation was built. We did seek FDA feedback on incorporating capecitabine, and at that point in the trial were discouraged from doing so.

I would also like to ask Dr. Hope Rugo to provide a clinical perspective on the role of adjuvant to capecitabine.

DR. RUGO: Thanks very much. This is actually a very interesting and important question. As you know, CREATE-X was done in Japan and Korea, and what we have found is that Asian patients can tolerate a much higher dose of capecitabine and 5-FU with less toxicity compared to Caucasian

patients, as well as other ethnicities.

For CREATE-X, they used the FDA-approved dose of capecitabine, which is not tolerable in our patients, particularly not in the post-neoadjuvant setting; and they found a benefit, as you know, that the benefit was primarily driven by patients who had triple-negative disease.

In clinical practice, we found that delivering capecitabine is very difficult after neoadjuvant therapy and after surgery due to toxicity issues, and also that the efficacy is difficult to see on a patient-level basis, where patients who have a poor response to neoadjuvant chemotherapy relapse either during or just after their capecitabine treatment in the adjuvant setting.

So I don't think that in clinical practice anyone who's treating patients with triple-negative breast cancer in this setting sees capecitabine as a solution to the poor outcome of patients who have high-risk, early-stage, triple-negative breast cancer.

DR. ARMSTRONG: Thank you, Dr. Rugo.

Can I have you pull up slide CE-19? I just wanted to just confirm the AE-related mortality.

In the pembro/chemo neoadjuvant phase, there were 5 deaths due to AE and there were 2 deaths due to AE in the adjuvant phase, which is a total of 7, which by my reading is a 1 percent mortality rate in the pembro/chemo arm due to AEs, and there's 1 out of 389 in the placebo/chemo arm.

Correct?

DR. GOODMAN: Yes. So as you say, 5 in the neoadjuvant phase and 2, so that's 0.9 percent versus 1 percent, keeping in mind there's a 2 to 1 randomization here.

DR. ARMSTRONG: Right, yes.

Question. Do you have outcomes based on BRCA status in the patient population?

DR. GOODMAN: We do not. Only a limited amount of data with respect to BRCA status is available at this time, and we do not have outcomes BRCAs.

DR. ARMSTRONG: Thank you.

I just had one final comment, which is the patient-reported outcomes in subjects who are randomized to a placebo after surgery who would not normally have to come into clinic every 3 weeks is a little bit -- I think one has to interpret that with caution because having to come into clinic and not receiving any active treatment every 3 weeks is actually something that would normally be a negative outcome.

But because both arms have to come into clinic, the PROs particularly in the adjuvant setting I think are not particularly reliable since they don't reflect the increased requirement for having to come in for treatment, since both the placebo and pembro arms have to do that.

That's just a comment. Thank you for letting me speak, and I'll be done here.

DR. HOFFMAN: Okay.

Dr. Portis, please?

DR. COMPAGNI PORTIS: Yes, thank you. This is Natalie Compagni Portis. I have a few questions.

One, do you have data that you can show us on response differences in post- and premenopausal women?

DR. GOODMAN: Response differences in premenopausal women and postmenopausal women with respect to the pathologic complete response rate?

DR. COMPAGNI PORTIS: Correct.

DR. GOODMAN: Okay. I will ask Dr. Valia Karantza to address that question, please.

DR. KARANTZA: Yes. This is Valia Karantza. I'm the clinical league for the breast program at Merck. That was one of our prespecified subgroup analysis, and we did not see differences in premenopausal versus postmenopausal.

DR. COMPAGNI PORTIS: And do you see any differences in response based on ethnicity, especially given the fact that we know that African American women are much more often diagnosed with triple-negative breast cancer?

Do you have any data based on ethnicity?

DR. GOODMAN: Dr. Karantza, you can take that one as well, please.

DR. KARANTZA: Yes. Thank you. In regards to ethnicity, we do have that as a prespecified analysis. There was not a prespecified analysis specifically on African Americans. We did not see any differences overlapping the confidence interval for subgroups based on ethnicity.

However I would like to mention that African Americans constituted only 4 percent of the total patient population, which is a total of 53 patients. This is too small a number to make any kind of analysis.

DR. COMPAGNI PORTIS: Yes, that makes sense. Thank you.

Then one other question perhaps for Dr. Rugo. Given what we're seeing in terms of the lack of strong data, especially regarding overall survival, who would you recommend this to now and why?

DR. RUGO: Okay if I answer?

DR. GOODMAN: Please go ahead, Dr. Rugo.

DR. RUGO: . Thank you.

Thanks for that question. I think it's a

really important one. As someone who treats a lot of patients with triple-negative disease in the neoadjuvant and adjuvant setting, we try to treat these patients in the neoadjuvant setting so that we get a better idea of response and can do our best to change therapy to try and improve response, as we know that this is currently a critical endpoint for the individual patient.

Based on the data that we have, as well as our own data from I-SPY2, I would treat patients who have node-positive more locally advanced disease and not a smaller node-negative tumor. I think these are the patients where we tend to see a higher chance of residual disease and a worse outcome in the long term.

Indeed, in triple-negative breast cancer, we don't have a good rescue. As I mentioned about the capecitabine, these patients tend to be younger and have very rapidly progressive disease. So I would choose to treat patients who have the highest risk because we really don't have any other way to salvage a poor outcome with poor response.

I think the survival data is important to mention. As was pointed out by the FDA, it's an early time point to evaluate overall survival; there just aren't enough events yet, and the event-free survival data is certainly compelling, although still not final.

DR. COMPAGNI PORTIS: Thank you, Dr. Rugo.

DR. GOODMAN: Thank you, Dr. Rugo.

If I may ask Dr. O'Shaughnessy, who I also would like to provide a perspective on use of this in practice.

DR. O'SHAUGHNESSY: Thank you. Thank you. I appreciate the opportunity to provide this. This is very important to me; Joyce O'Shaughnessy, Baylor University Medical Center, breast medical oncologist.

I focus my clinical research efforts on triple-negative breast cancer, and as a result, my patient population is enriched for triple-negative breast cancer. As I was reading the FDA briefing document, I was glad to see where it said that regulatory decisions can take into account outcomes

in important subgroups.

The clinically node-positive subgroup in triple-negative breast cancer patients that are going to get preoperative therapy is an extremely high-risk population. They do much more poorly with regard to pathological complete response rates of entry and overall survival. It is a mesenchymal biology that allows them to become node-positive and also is associated with more drug resistance, chemotherapy resistance.

In IA3, the pathologic complete response delta in the node positive was 12 percent, and it's stable because it was 13 percent in IA2. As we saw from the slide that had been shown by both Hope and Valia, there is a very strong patient-level association between achieving a path CR and event-free and overall survival.

In KEYNOTE-522, the patients with a path CR with pembrolizumab did really remarkably well. So that 12 percent delta in the node positive is important, and the event free survival in the node positive in IA3 is 0.69, and that's supported.

That positive benefit on event-free survival is supported by the positive impact of pembro in other very high-risk patients in KEYNOTE-522, stage 3 disease, those with no path CR; residual cancer burden 2, which is a lot of cancer left after preoperative therapy, and that was 20 percent of the patients. That was the biggest group aside from pathology RCB-II, a big impact on event-free survival.

Also, a CPS PD-L1 expression less than 1, that's a very poor prognosis group. They only had a path CR rate with chemotherapy of 39 percent in KEYNOTE-522, and the event-free survival hazard ratio was 0.4 in those patients.

Now on the other side of the coin, the serious and long-term enumerated AEs, which can rarely be fatal, are just never acceptable. But in my mind, the benefit-to-risk analysis greatly favors pembrolizumab in the most high-risk, triple-negative, which is exemplified by the node-positive population. And I find this 12 percent delta IA3 in the node-positive to be of

very high clinical relevance and very clinically actionable now in my practice.

Lastly, it's strengthened by what we've seen in other checkpoint inhibitor preoperative studies in triple-negative patients, where also the node-positive population have had a big delta on their path CR. So I think it's very important right now in my practice. I really wanted to emphasize this most high risk of population. Thank you for allowing me to.

DR. GOODMAN: Thank you, Dr. O'Shaughnessy.

DR. COMPAGNI PORTIS: Thank you for all of that. I just want to clarify, though, that's all really important information, though it sounds like you're talking mostly about PFS and EFS, not about overall survival.

Is that correct?

DR. O'SHAUGHNESSY: Yes. I think the overall survival data, in my opinion, are too early at this time point to interpret. So I'm looking at the path CR rate of 12 percent, which on a patient-level basis, 12 percent of node-positive

patients, if they get a path CR, it's so compelling because the event-free survival -- and I shouldn't have said survival.

You're correct. I should not have said that. I should have said event-free survival. In other studies, it's overall survival, too, but in KEYNOTE-522, it's event-free survival, where there's a very tight relationship.

DR. COMPAGNI PORTIS: Thank you very much.

I --

DR. HOFFMAN: Dr. Ellis? Oh.

DR. COMPAGNI PORTIS: Thank you.

DR. HOFFMAN: Dr. Ellis, you're next.

(No response.)

DR. HOFFMAN: Okay. Let's move on to Dr. Seidman then.

DR. SEIDMAN: Thank you. I think Dr. Ellis -- oh, he just unmated, if you want to go back to Dr. Ellis.

DR. HOFFMAN: Okay.

Dr. Ellis, please?

(No response.)

DR. SEIDMAN: I'm happy to jump in. This is Andrew Seidman from Memorial Sloan Kettering.

DR. ELLIS: Yes. It's Matthew. Sorry. I had connectivity problems.

DR. ELLIS: Okay. Go ahead, Matt.

DR. SEIDMAN: Yes. Deep apologies. Sorry.

I just wanted to push back slightly on the capecitabine discussion because I don't think Dr. Rugo's comments are widely accepted.

The current NCCN guidelines say consider adjuvant capecitabine in patients who haven't had a pathological complete response. And the issue of dose tolerability has recently been addressed, at least in part, by a second study, recently published in the Journal of Clinical Oncology, showing the drug may be effective at lower doses, indicating if you have to dose-reduce because of toxicity, you can still anticipate efficacy.

So my question is, given the NCCN guidelines indicating capecitabine should be used in the non-path CR setting, or at least considered, if patients are going to receive pembrolizumab, are

you suggesting a delay in the capecitabine, or are there data that says that capecitabine and pembrolizumab are safe in combination? Because we sort of have two conflicting clinical practices if pembrolizumab is approved.

I'll stop there. Thank you.

DR. GOODMAN: So as you've heard, there are some conflicting data for the use of capecitabine in the adjuvant setting and its use in clinical practice.

I'd like to ask if Dr. Aditya Bardia would like to provide some additional clinical perspective on the role of adjuvant capecitabine as it relates to the use of pembrolizumab in this setting, based on the 522 data.

DR. BARDIA: Thank you very much. I can provide comments related to the use of adjuvant capecitabine. As has been mentioned earlier, CREATE-X trial demonstrated that the use of adjuvant capecitabine is associated with improvement in recurrent-free survival or event-free survival as compared to no treatment, but that

trial was predominantly done in Japan in an Asian population. The trial has not been replicated in the U.S., although the use of adjuvant capecitabine is listed in various guidelines, including NCCN.

In terms of the impact on KEYNOTE-522, as was mentioned earlier, when KEYNOTE-522 was designed during the execution of the study, adjuvant capecitabine was discussed, but it was discouraged to use adjuvant capecitabine because it would further complicate the study and make interpretation of both neoadjuvant pembro as well as adjuvant pembro difficult.

So at this time, we don't have any data to suggest that capecitabine after pembro or with pembro, how that would impact the event-free survival.

We do have safety data, though, and it's predominantly in the metastatic setting, where the combination of capecitabine plus pembrolizumab is safe. So at least from a safety perspective, there's no concern with the combination of capecitabine along with pembro.

DR. HOFFMAN: Okay.

DR. GOODMAN: Sorry. I was on mute.

Thank you, Dr. Bardia.

DR. HOFFMAN: Does that wrap up your questions, Dr. Ellis, at the moment?

DR. ELLIS: Well, I just want to emphasize in this area of uncertainty with both drugs, I think we have a result with a drug that's replicated in several clinical trials, although acceptance not in a European-American population; then we have a second drug with uncertainty as to its long-term efficacy.

So there's a lot of uncertainty right now as to what the clinical practice should be, and I'll stop there.

DR. GOODMAN: I believe Dr. Rugo would like to make a couple additional comments on this issue before we close.

DR. RUGO: I just wanted to comment back about the recent trial -- the Chinese trial, I believe is what Dr. Ellis is referring to -- where patients received continuous dosing of capecitabine

with early-stage, high-risk, triple-negative breast cancer treated in the adjuvant setting.

I think that we were all very impressed when that data was presented, and now it's been published, and thought this might be a way to get around some of the toxicity issues that we see in Caucasian patients, and I have to say some other ethnic groups in the post-neoadjuvant setting.

Having now tried that regimen with several patients, I would argue that we have the same problem. I have not had a single patient tolerate the regimen. In fact, the toxicity is greater than I have ever seen with the lower dose that we've used trying to replicate CREATE-X.

We use a dose that is the sort of Caucasian dose for capecitabine, which is not the same as was used in CREATE-X, and by trying to give a lower dose continuously, it just has been really undoable. So I think it is quite fascinating data that was in a Chinese population, and although it hasn't been studied well, there may again be very significant differences in metabolism of 5-FU.

DR. ELLIS: Well, it's Dr. Ellis. I have to respond to that. Your anecdote through clinical experiences is highly relevant here, and I would say I have the contrary view that it's a tolerable regimen. So I'm not sure there's agreement on that point.

DR. HOFFMAN: Okay. I think we probably don't want to get too far into the granularity of the specifics of the capecitabine, but I know that it's relevant in the bigger picture here.

Let's move on to Dr. Seidman.

DR. SEIDMAN: Thank you. This is Andrew Seidman from Memorial Sloan Kettering. First, I just want to thank the FDA and the applicant for what were really clear and concise presentations. Actually, I have three questions.

The first is for the applicant, and it relates to the extent of disease evaluation performed in patients with clinical stage 3, triple-negative breast cancer. Forgive me if I missed it, but was this protocol stipulated, and what actually happened in terms of ruling out

occult metastatic disease?

DR. GOODMAN: So you're asking about the evaluation of disease at baseline in patients with stage 3 breast cancer; is that correct?

DR. ELLIS: Yes, node positive perhaps, or certainly stage 3, clinical stage 3 patients who we know have the certain likelihood of having occult stage 4 disease. Were they required to have certain types of imaging before entering the trial to rule out metastatic disease?

DR. GOODMAN: Sure. I'll ask Dr. Karantza to address that, please.

DR. KARANTZA: Yes. This is Valia Karantza, clinical lead for the breast program at Merck. We did not require mandatory baseline scans. What we did is we followed clinical practice and guidelines per NCCN and other oncology groups. Actually, it is the clinician's discretion to perform such screening.

DR. SEIDMAN: Thank you, and just one quick follow-up question.

Do you happen to have data on whether there

was balance between the two arms and whether patients were assessed for metastatic disease?

DR. GOODMAN: Dr. Karantza?

DR. KARANTZA: I cannot answer your question right now. We have been collecting, wherever it was performed, baseline stage in CAT scans, but this has been collected and held, so we have not evaluated them ourselves.

DR. SEIDMAN: Thank you.

My next question is also for the applicant, and it relates to event-free survival definition. I'm wondering if the applicant could comment on the positive margin at the time of surgery as an event, what this means in terms of downstream events, and whether there's a precedent for including that as an event.

DR. GOODMAN: Right. As you note, we did include margins at the time of last surgery as EFS events. Again, I'll ask Dr. Karantza to comment on why that was included in the implications and perhaps also to share a sensitivity analysis that we did where we excluded those events.

DR. KARANTZA: Yes. As mentioned by us and as acknowledged also by FDA, there is not a universal EFS event definition. What we did actually is we took the most conservative approach, as positive margins at surgery are associated with an increased risk for local recurrence and eventually distant recurrence.

The way we defined positive margins was, again, the most conservative, it was tumor, I think, or in-tumor [ph], which essentially meant that there was likely tumor cells left behind after surgery. What we have done is we did a sensitivity analysis where were excluded -- we did the EFS analysis where we excluded positive margins. Slide up, please.

This is our sensitivity analysis, and this has a hazard ratio of 0.68 with confidence intervals of 0.5 to 0.92. In this occasion, rather than having a positive margin as an initial adverse event, if these patients developed any adverse event, a later event of a local or distant recurrence, but the one was counted.

I would like to mention that we had a total of 16 patients with positive margins at surgery, and half of them within the IA3 time follow-up had already distant recurrence and one had the local recurrence. So there is a very high incidence.

DR. SEIDMAN: Thank you. You've answered that very well.

My final question -- and I guess I would also invite Dr. Berry maybe to weigh in on this -- relates back to the foundation chemotherapy regimen. We had discussed earlier about some heterogeneity in real-world clinical practice regarding the incorporation of carboplatin.

I would also submit that there's heterogeneity with respect to the schedule of anthracycline. Dr. Berry authored a paper many years ago showing the benefit of dose-dense adjuvant therapy with anthracyclines in the adjuvant setting.

Recognizing it would be challenging to marry a q3-week antibody with q2-week chemotherapy, I'm just wondering if the applicant or Dr. Berry would

want to weigh in on the issue of optimization of chemotherapy, not with respect to carboplatin, but anthracycline schedule.

DR. GOODMAN: As you note, dose-dense anthracyclines were not provided as an option due to the additional toxicity and the inconsistency of use between the regimens.

I will also ask, since you brought up Dr. Berry's publication, if he would like to comment further on that question.

DR. BERRY: Thanks. I'm Donald Berry, consultant for Merck through a contract between Merck and Berry Consultants, a company I co-own. Neither Berry Consultants nor I have a financial interest in the meeting outcome.

Thanks for the question. The only thing I can add is that this was done in both groups, so presumably it would even out. But I don't have anything further to add.

DR. GOODMAN: Thank you, Dr. Berry.

Perhaps I can ask for a more clinical perspective on the choice of chemotherapy regimens

from Dr. O'Shaughnessy.

DR. O'SHAUGHNESSY: I'll just provide a perspective on the question that Andy asked, and that is that the Oxford overview meta-analysis has clearly shown that a dose-dense regimen in the breast cancer curative setting is superior to a non dose-dense regimen. So it's become the standard of care to use AC pretty much every 2 weeks, and this KEYNOTE-522 uses it every 3 weeks.

We had a lot of discussion about that in our U.S. oncology breast committee. There was consternation around that. We looked carefully at the Oxford overview analysis, and they looked at regimens overall. They didn't break down the anthracycline portion of it versus the taxane portion of it. It was just overall.

The trial that is there that can help us in this regard is the TAC-2 trial from the UK or the 2 by 2 factorial design. One of the randomizations in the early-stage breast cancer HER2 negative was an every 3-weekly versus an every 2-weekly

EC regimen, with a subsequent randomization on another question, and there was no difference in the outcome for the patient for q3 and q2.

So I personally felt comfortable with the every 3 weekly, but Andy's point is well-taken that the dose-dense regimen is the standard of care across the country.

DR. SEIDMAN: Thank you, Joyce.

I have no other clarifying questions. Thank you for the time.

DR. HOFFMAN: Okay. Why don't we take a break at this point, and we'll have an opportunity for more clarifying questions after the open public hearing portion. Let's take a break now and resume at 12:45, please. Thank you.

(Whereupon, at 12:28 p.m., a recess was taken.)

Open Public Hearing

DR. HOFFMAN: We will now begin the open public hearing session

Both the FDA and the public believe in a transparent process for information gathering and

decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance

in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. DINERMAN: Good afternoon. My name is Haley Dinerman, and I'm the executive director of the Triple Negative Breast Cancer Foundation. I thank you for the opportunity to speak here today about the unmet medical need for therapies in high-risk, early-stage, triple-negative breast

cancer.

Please note that I've not been compensated in any way for my remarks. I'm here as an advocate who works closely with TNBC patients and their families, and I hope to give a voice to a community of breast cancer patients that is often overlooked.

I co-founded the Triple Negative Breast Cancer Foundation in 2006 when my friend Nancy was battling triple-negative disease. At the time, very little research was being done in this area, and there were very few places to turn for guidance and support. Fortunately, that is no longer the case.

Since its founding, the TNBC Foundation has grown to be the leading advocacy group for the triple-negative community. We fund TNBC specific research, we offer resources and support to TNBC patients and their families, and we work to make sure that the unique needs of the TNBC community are understood and considered, which is why I appreciate the opportunity to lend my perspective to this discussion.

I've seen firsthand how devastating this disease can be. Despite giving it everything she had, Nancy died of TNBC at just 37 years old. She left behind a close-knit family and many friends who struggle with her loss to this day.

Nancy was the first of many devastating losses I witnessed. Through many years of work with the TNBC Foundation, I developed close relationships with the community I serve. I've made many friends over the years who've lost their lives to this horrible disease.

My friends Fern Dixon and Annie Goodman are two such examples. Fern was 43 years old when she died and Annie was just 33. Another friend was Lori Redmer. She was the TNBC Foundation's former executive director. Despite having every possible connection and resources at her disposal, Lori was also unable to fight off this disease. She died in her early 40s as well, leaving behind a husband and three young daughters.

I want you to see their faces and the faces of these friends that I lost too soon. I want them

to be in this virtual room with us today. These women were all in the prime of their lives, and they deserved better.

These are the faces of the women we serve. They're strong, they're fighters, they're willing to do what it takes to battle this beast, but they need options, especially for high-risk, early-stage disease.

The TNBC Foundation hears regularly from thousands of triple-negative patients. Our online discussion forums have nearly 10,000 registered users. Our official private Facebook group has 9800 active members. We host regular TNBC Community Zooms, and we engage with patients and hear from them directly.

As an organization, we have our ears to the ground and we know this patient population. We hear their fears and understand their desperate need for more treatment options. For those diagnosed with high-risk, early-stage disease, there are no targeted therapies.

These women and their families would give

anything for more choices. They tell us how demoralizing it is for them to attend non-TNBC specific support groups, or to sit in, in their doctors offices or chemo units, where they hear about the treatment options available to other breast cancer patients, but not to them.

While fortunately the treatment landscape is developing for women with metastatic TNBC, for the early-stage patient, there are incredibly limited options. When a therapeutic option presents itself, it should be available for consideration in the clinical setting. Patients in consultation with their doctors should have the option to choose.

The TNBC community is disadvantaged enough compared to other breast cancer patient groups, given that many of the greatest breakthroughs in breast cancer treatment do not apply to them. Within the overall TNBC patient population, there are certain defining characteristics.

Triple-negative breast cancer often strikes younger women, women of BRCA gene mutations, women

of Ashkenazi Jewish descent, and women of African American descent. The data relating to black women with TNBC is especially concerning. Black women are 2.3 times as likely to be diagnosed with TNBC and far more likely to die of this disease, which is clearly unacceptable.

As TNBC patients are more commonly in the prime of their life when diagnosed, I could argue that based on expected lifespan, triple negative is the most costly breast cancer in terms of unrealized years of life, given the typical young age of onset and the all too frequent early death.

Patients with high-risk, early-stage TNBC should have the option, together with their medical team, to consider a therapy that might prevent their cancer from advancing. I'm sure you agree that these patients deserve to have as many weapons in their arsenal as we can safely offer them.

I want to thank you for taking the time to listen. I hope I was able to give you some insight into the very real unmet need faced by patients in our TNBC community. We desperately need more

therapeutic options, especially in the high-risk, early-stage setting. Hopefully today we'll be closer to having one. Thank you in advance for your consideration.

DR. HOFFMAN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. FAIRLEY: My name is Ricki Fairley, and I'm the founder and CEO of TOUCH, The Black Breast Cancer Alliance. Thank you so much for the opportunity to speak today about meeting an unmet medical need for early-stage TNBC. I'm very blessed to be approaching 10 years of survivorship of TNBC. I'm not being compensated for giving my remarks today, and our foundation has not received any grants from Merck.

When I researched TNBC after my diagnosis in 2011, I found only bleak news. As I'm sure you know, TNBC is associated with the worse prognosis and low overall survival rate, and there are

currently no treatment options for early-stage TNBC. TNBC patients are fighting in a war with absolutely no weapons.

I was given a death sentence with no hope. For my stage 3A TNBC, I had a bilateral mastectomy, 6 rounds of TAC chemo, and 6 weeks of radiation. And a year to the day of my diagnosis, a PET scan identified 5 spots on my chest wall. My oncologist told me that I was metastatic and to get my affairs in order because I had two years to live. He had only seen two cases of TNBC, and both patients died within nine months.

I was not ready to die, so I took matters into my own hands. I reached out to the TNBC Foundation, who directed me to Dr. Ruth O'Regan at Emory. Dr. O'Regan suggested a regimen of carboplatin and Gemzar. After 4 rounds of that treatment, I miraculously had no evidence of disease.

Obviously, God had another plan for me and gave me my purpose. I know that God left me here to do this work and help my breastees get through

breast cancer. I've been an advocate ever since I was sick, and I fight like a girl every day to eradicate this disease that disproportionately affects women who look like me.

TNBC is a different disease. Because TNBC is the only breast cancer that doesn't have a drug to prevent recurrence, we fight a different fight. As I started pursuing the data and engaging in the breast cancer advocacy community, I could see the impact on black women. There were no national studies about TNBC in black women until just a few years ago when Dr. Lia Scott at the University of Georgia conducted the first one, indicating that black women are 2.3 times more likely to be diagnosed with TNBC.

That was the foundation of my pursuit to study and label black breast cancer. The prevalence of TNBC in our community is a large contributor to the devastating statistics for black women and breast cancer. Let me break down for you what black women are facing.

Black women have a 31 percent breast cancer

mortality rate, the highest of any U.S. racial or ethnic group. Black women are 42 percent more likely to die of breast cancer. Black women under the age of 35 get breast cancer at twice the rate of white women and die at 3 times the rate. Twenty-one percent of black women with breast cancer don't survive 5 years past their diagnosis compared to 8 percent of white women. Black breast cancer survivors have a 39 percent recurrence rate, higher than white women.

The physiology of black women has not been a high consideration in clinical trial research, and on January 21st of 2021, JAMA Oncology published an article stating that the risk of death for black women with breast cancer is 71 percent higher than for white women. These statistics are just unacceptable. Black women deserve better.

I founded TOUCH, The Black Breast Cancer Alliance, to bring attention to the science and to bring the health of black women into breast cancer research conversations. My purpose, passion, and mission is to eradicate black breast cancer. At

TOUCH, we are working to ensure that the medical research community uses culturally competent language and behavior to recruit black women into clinical trial research. This is an uphill battle, given that all the work to date, despite great efforts and a lot of money, have only managed to garner a less than 5 percent participation rate by black women in clinical trials.

As you look at the faces of my TNBC breastees, know that a drug like Keytruda could have stopped their cancer from advancing and possibly given the dead ones a better outcome. I'm ecstatic to have Keytruda as a potential new therapy for early-stage TNBC. There are currently no treatment options in our space. This is a much needed first, our first and only weapon in a horrific war.

Though the trial results are highly favorable, as breast cancer patients we are always in a trial. We never know for certain that a treatment will work for us. I greatly appreciate the work that you do, but the way I see it is that

you have the power to bring hope over fear, years of life over months of life, a chance to see a child grow up, a chance to meet a new grandbaby. I don't even want to think about how many women will get advanced disease, and even die while waiting for this life-saving therapy. Think about how you would feel if one of your family members were at risk.

In addition to saving lives, you can bring real and genuine hope to a very bad situation. You have the power to change the course of TNBC and impact many lives, and the time is of essence.

I have two brilliant daughters, two perfect granddaughters, and a third grandbaby due in March. The risk of death if any one of them were to get breast cancer is 71 percent higher than for white women. As a mom and a grandma, I'm incapable of accepting that. They are my daily inspiration, and I have about 10 years before Belle [ph], my oldest granddaughter, has breasts. My goal is to put myself out of a job by then.

I appreciate your time and this opportunity

to share my story. Frankly, Keytruda for early-stage TNBC cannot get to the market soon enough. Thank you in advance for helping me reach my goal for Belle, the other women in my family, and the black breast cancer community.

DR. HOFFMAN: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. KARMO: My name is Maimah Karmo. I'm with the Tigerlily Foundation. I have not been paid for these remarks. I share my story today in honor of my friend who are black women who are not with us today.

In just the past two months, we lost Chawnte in December, Nani [ph] on last Sunday, and Sarah just four days later, all leaving behind children, husbands, and friends. Before Nani died, she called me in tears, struggling for breath. She was not ready to go, but she died 3 days later. They won't see their kids grow up, get married, or

live their lives.

After I heard the words, "You have breast cancer," I was terrified. Black women have worse outcomes who look like me. The outcomes are grim. I was given AC and Taxol and told to go live my life, yet, every month, somebody I know dies and suffers. Treatments feel as time, and time again. Imagine this. You're being attacked by unseen gunmen, yet you stand there defenseless. This is what my friends and I feel like every day.

As a patient, I fought in the face of fear of cancer cells that may someday attack my body again. As I watch my friends suffer and die, I wonder how many more will lose their lives or when it will be my turn to die.

While I understand your concerns about this new drug, all we want is more time with loved ones. Our lives are not about charts, graphs, or data. The sooner you attack cancer, we have a better chance at outcomes and at life. No amount of time or life is too small to save or too small to live, and we deserve better, and we deserve more. We

need better treatment options now because our lives cannot wait. Thank you.

DR. HOFFMAN: Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. PERELLO: Hello. My name is Kristen Costa Perello. I do not have an affiliation with any organization. In opening, I'd like to state that I am not receiving compensation to share my experience here today, and I also do not know whether I actually received pembro as part of the clinical trial; and from what I understand, I will never know that. I'd like to think that I did based on the positive experience I had during chemo, and now I will share my story.

I was diagnosed with stage 2 invasive ductal carcinoma TNBC cancer in August 2017 at the young age of 35. I underwent 16 rounds of chemotherapy treatment starting in September 2017, including the clinical trial for pembro. I had a double mastectomy with reconstruction the very same day in

March of 2018 and received radiation therapy ending in June of 2018.

I'm so happy to say I have had no evidence of the disease since June of 2018 at the conclusion of radiation. I saved my hair during chemo with the use of cold-capping therapy, and dressed up, and wore high heels to every treatment. My motto was, "High heels and high spirit," as you can see on the slides here. I'll explain the slides at the end. I'm still so proud of what that motto means, and I will always cherish that.

I did a couple of local news segments to share my story of this motto and how well I did during treatment through local attention. I was connected to Dr. Joyce O'Shaughnessy through my breast surgeon in Fort Worth, Anita Chow. Dr. O'Shaughnessy is known to attend a lot of speaking events and be involved in many clinical research projects to help breast cancer patients, and I will never forget that first appointment I had with her.

She made the time for me before one of her

travels and saw me for an appointment at 6:30 p.m. in Dallas. I lived in Fort Worth at the time. It was then she told me about the clinical trial she had happening for pembro and drew up a plan for my treatment. I read through the trial documents and took my time. I signed up at my next appointment. I immediately trusted Dr. O'Shaughnessy. I thought to myself, "Why wouldn't I want to sign up for something that could potentially give me better success with my treatment outcome?"

I started on the clinical trial day 1 of chemo in September of 2017. I had a complete response to chemo after my third of 16 treatments, and my lump could no longer be felt. Throughout my chemo treatments and until the clinical trial ended for me in December of 2018, I had honestly never felt so good in my life. I felt better on chemo than off of it. I often tell people that. They think it's amazing and a little crazy. And really, looking back, so do I.

Of course the strict diet I implemented was a huge proponent of this. I rang the bell and

finished chemo in February of 2018 and ran a 5K the same week. I then rang the bell again in December of 2018 with my new boyfriend and sister by my side, and that was the last day that I received the pembro or placebo injection.

I felt good enough to be in the gym throughout chemo about 3 days each week, even on the harshest treatment of all, the "red devil." I will be forever grateful to my support system and what I like to call my dream team of doctors, with Dr. O'Shaughnessy at the forefront of that.

In talking with other women in a local breast cancer group that I am still a part of, their doctors weren't always as aggressive with treatment. I know everyone has different cancer profiles, but I'm glad and lucky that mine fit the profile so I could partake in the trial.

It truly takes a village to get through the emotional roller coaster in the dark times a cancer diagnosis presents, as well as financial burden. Only those who have been diagnosed understand what it's like to hear those words, and follow, and go

through that journey. Even then, everyone has different journeys and different hard parts. My hardest part was radiation and the wounds that came along with those treatments.

While I do not know, as I stated before, whether I received pembro, and likely never will, I like to believe that I did because I felt so incredibly good during chemo and never had sickness; only a few days during the red devil treatments where I went to bed earlier than I normally would.

Now I'm living in Seattle. I just moved here last week. I've married the love of my life, who I met at the tail end of treatment, and we just had a beautiful baby girl, and she's very healthy. She was born in early November. Her name is Ava. I was able to get pregnant naturally right after coming off of the IUD, although I did freeze my eggs before treatment started due to the unknown of whether I'd be able to conceive. With what my body has been through, I thought I could potentially have a long fertility road ahead of me. My husband

and I hope to have another child within a couple of years.

I love to travel, pre-COVID of course, cook, hike, work out, visit with family and friends, and live my best and healthiest life every day. And I truly believe that my treatment path has helped me get to where I am now and helps me live a prosperous life every day. I feel like I've been given a second chance.

I maintain a full-time job, which I'll return to in April once maternity leave ends. I often like to remind women and men to check themselves and listen to their bodies and any signs of changes. I also like to remind people to be advocates for their health and ask a lot of questions.

I'm proud to say I'm still connected to my breast cancer groups and help other women advocate for themselves and their treatment tasks. Please help us get this drug approved. I think we can all agree that it's important for high-risk, TNBC breast cancer patients to have more treatment

options, and pembro offers that. Thank you for listening to my story.

For the pictures, I have explained. A lot of them were during treatment. The first slide shows when I rang the bell in my last days of treatment, as well as when I ran the 5K.

Next slide, and this is my last slide. This is my life now with my beautiful daughter Ava and my husband, and living a healthy and prosperous life. Thank you for listening.

DR. HOFFMAN: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. BRYANT: Hello. My name is Jillian Bryant. I wanted to start by saying that I have not received any financial compensation for my participation today.

It is my great honor and privilege to speak to you, and I thank you in advance for listening to my story. I live in Lake Stevens, Washington, just

north of Seattle, and in August of 2018 at the age of 39, and after only one year of marriage, while trying for our first baby together, I lay there in bed with a deep ache on my left side, and that is when I found the lump that ironically was 4 years almost to the day that I had lost my older sister at the same young age of 39 from esophageal cancer.

As you can imagine, our lives were forever changed, and now I was facing the same ugly disease in a different place within my body, and afraid just does not begin to describe my horror. Somehow, I had to seek a way not to follow in my sister's footsteps.

I was diagnosed with stage 2 invasive ductal carcinoma. But that was not all. It was triple negative, and as you know, triple negative does not have the many options that hormone-positive cancers do. Therefore, this rare aggressive diagnosis leaves those that hear those words with an unexplainable fear and in a constant state of anxiety.

Because Keytruda is unfortunately not yet

standard protocol for early TNBC, I was extremely fortunate that my Seattle oncologist was cutting edge and knowledgeable to ensure that I had this drug as an option, not within a trial, but the actual Keytruda drug. I was fighting for my life and I needed to ensure we were doing everything we possibly could to combat this aggressive diagnosis.

I strongly believe that every weapon in the oncologist arsenal should be offered to qualifying breast cancer patients. My oncologist got an early start on the process. My medical insurance denied Keytruda. We appealed the paperwork, and Merck approved me on the Patient Assistance program.

I received 4 Adriamycin/Cytoxan and 12 Taxol/carboplatin chemotherapies, and similar to a clinical trial regimen, we added the Keytruda after the AC when I began the TC chemo treatments. I received Keytruda every 3 weeks for 12 months. After chemo, I had a lumpectomy, followed by a bilateral mastopexy, and my surgery result was great. I had clear margins and no lymph node involvement.

We were thrilled. I went on to do radiation and continued Keytruda for the 12-month duration, and I had no side effects from Keytruda. And I should note that I worked the entire time during my treatment, as I'm the sole provider for our family, and working equals my medical insurance. But to be honest, we would have lived in a cardboard box and sold everything that we own to get Keytruda as part of my regimen. But gratefully, because of my oncologist and the Merck Patient Assistance Program, it made it possible for me to receive this immune therapy with the most beautiful outcome: my health and my future.

Keytruda literally was the key to my survival and to accompany the chemotherapy regimen in my treatment. And along the way, I met many other breast cancer patients, most of which were hormone positive, and they had so many more options in their arsenal such as tamoxifen or Herceptin. But in my mind, Keytruda is the equivalent to that, and all TNBC patients should not have to hear, "Oh, that's not protocol," or "Denied," from their

insurance company, or worse, to not even have it be brought up by their oncology team as an option.

It is my hope and prayer that every candidate for Keytruda has the opportunity to receive this medicine to truly change the trajectory of their prognosis. But they don't need to fight for their life and fight for the medication and their insurance company.

It is my hope that the oncologists and the decision-makers on this call today hear these words and think of Keytruda whenever it could favorably impact a patient with this diagnosis, for you to hear from someone who directly benefited from the Keytruda drug. But I'm endlessly and eternally grateful from the bottom of my heart for this life-saving drug.

I'm happy to report that I am 43 years old now. I'm doing very well. I'm working full-time and so thrilled to say that I'm 12 weeks pregnant. When I was diagnosed in 2018, I asked myself, "How?" "Why?" "Why is this happening to me?" "How could this happen to our family a second

time?" And today, at this moment, speaking for the people who will decide if Keytruda can be offered to other people going through TNBC, I know that this, this moment right now, is the reason why; so that my words could be the words that you hear to decide that Keytruda should be readily available, and covered by medical insurance, and part of the protocol for all stages of TNBC patients.

When the commercial for Keytruda comes on TV, one day I want to hear "breast cancer" at the end, as it approves cancer, too. Wow! Because then I will know my silver lining and my why has been answered. I'll never be able to express how grateful I am that I've received Keytruda and to my oncologist, because thank you is just not enough for this gift.

In conclusion, my speech today is dedicated to the memory of those that we've lost, to those that are in the midst of their fight, and those we still have to save. With sincerest gratitude, I thank you for your time and your consideration today. Thank you.

DR. HOFFMAN: Thank you.

Speaker number 6, your audio is connected now. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WEISS: Good afternoon. I'm Dr. Marisa Weiss. I'm founder and chief medical officer of Breastcancer.org. I'm also an oncologist in practice for now over 30 years. I've received no compensation for speaking here today, but in the interest of full disclosure, Merck is one of many Breastcancer.org corporate sponsors that provide grants for content initiatives of which we are in full editorial control.

As chief medical officer of Breastcancer.org and as a practicing oncologist, I'm pleased to have this very important opportunity to speak on behalf of the thousands of women in the United States living with triple-negative breast cancer at this very moment.

For 20 years, the mission of Breastcancer.org has been to empower people with

breast cancer to make the best decisions for their care by providing free medically-reviewed information and peer support. Through a variety of resources, we reach out, educate, and support.

We also host a comprehensive online peer community with women and men from all over the world, who help each other cope with the challenges of breast cancer. This year alone, 21 million people have utilized Breastcancer.org's information resources and peer community.

Imagine being diagnosed with breast cancer and then finding out you have triple-negative disease; just that name, that name. We never wanted to name it that, but that's the name that it has, and it can really feel like a death sentence, and for too many people, it is.

Today, I want to focus on three key factors of triple-negative breast cancer that illustrate the urgency of developing novel strategies to manage this disease subtype more effectively.

Number 1. As you've heard, black and Hispanic women are disproportionately affected. As

everyone is aware, black women have the highest rate of new cases of triple-negative breast cancer. Recent events in our country have awakened a renewed commitment to confronting the harms of discrimination and disparities in every corner of society and boldly pursuing equity. Health care is no exception.

If we want to achieve health equity, as many of us have pledged to do, we must promote research and drug development for the conditions impacting minority communities most, including triple-negative breast cancer.

Number 2. Triple negative breast cancer is more likely to be diagnosed in people under age 50. This disease devastates young families as you've heard today. We need to do more to prevent the unimaginable heartache and loss that they experience.

Number 3. The standard of care for triple-negative breast cancer is simply inadequate at this point. The typical treatment of chemotherapy, surgery, and radiation can be both

debilitating and ineffective for too many women. We must do better.

Triple-negative breast cancer is more aggressive, has a poorer prognosis, and is more likely to metastasize and recur compared to other types of breast cancer. As an oncologist, I want to be able to look at my patients in the eye and give them reassurance and hope for new and improved treatment options that deliver better results. Their lives and their futures depend on it.

The words of Margaret, a member of the Breastcancer.org community, say it all. Quote, "It is sobering to realize that my subtype of breast cancer has the worst prognosis for duration of survival," unquote. Sobering and daunting; that's the everyday reality for too many people who are in desperate need of new and better options.

Thank you so much for allowing me the chance to share with you today, on behalf of Breastcancer.org, why we need to take immediate action to better help everyone affected by triple-negative breast cancer to overcome their

diagnosis and live a full life. And I can say on behalf of Breastcancer.org and our other partner advocacy organizations, that when this new treatment option or other treatment options become available, we will be there to make sure that any woman affected by this disease will get the benefit of these discoveries. Thank you.

DR. HOFFMAN: Thank you.

Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. GELBART: Good afternoon. My name is Suzanne Gelbart, and I am one of the participants of this clinical trial. I have not received any compensation for speaking here by a company or an individual.

In late January of 2018, at age 43, my husband found a lump in my left breast. Two days later, I was told that despite no family history of it whatsoever, the 3-centimeter foreign mass was breast cancer, and triple negative at that. My two

children were teenagers at the time. My career was humming along. I was involved in volunteer work with their high school and the National History Museum in Los Angeles every single week.

I had a very full life going on, but cancer is quite an inconsiderate thing. There were no options for me. It was chemotherapy, surgery, and possibly radiation, or I was going to die.

When I first met with my oncologist, she told me that I qualified for this clinical trial, and I did not hesitate. So I jumped in. Yes, chemo; yes, trial; yes, surgery; yes, yes, yes. Whatever you tell me I need to do, I will do it because I am lost.

Ten days after my diagnosis, after the whirlwind of scans and ports and chemo 101, I began treatment and the process of designing my life around blood draws, and infusions, and days of exhaustion.

My experience with cancer is terrifying, and humbling, and very boring. I of course don't actually know if I was given the drug or the

placebo. My clinical results, though, were pretty remarkable, at least to me. Six weeks after I began treatment and the trial, not even halfway through the first course of chemotherapy, my tumor was completely gone. Only the marker that was put in it was visible on the scan.

At that point, there were still many, many months and two major surgeries to go, and I was still reeling from going bald and trying to manage all the physical side effects that go along with chemo, while still grappling with all of the, "is there anything unfinished in my life?" kind of thoughts. But having that ultrasound that said no cancer seen so early on in my treatment was a lifeline to hope and a much-needed emotional boost.

My wish is that everyone working on this trial only knows cancer through numbers and data points, but in reality, this trial is about much more. It's moms getting to see their children graduate high school. It's women getting to become mothers. It's women being able to have the career that they dreamed of. It is about hope over

heartbreak, and that's what it gave to me at least.

I had my latest scan last week, and it was all clear. I am now two and a half years cancer-free, and each month that goes by, as I get closer to that holy grail of the three-year mark, I breathe a little easier.

In closing, I want to tell everyone today how grateful I am for all the work you do to help women like myself. It's my sincere hope that by participating in the trial, maybe I have done some good for someone else's future, as well as my own. I believe that clinical trials like this one are where the biggest and sometimes only strides are made against diseases; and that eventually trials like these become the standard of care and absolutely save lives. Thank you for listening.

DR. HOFFMAN: Thank you.

Speaker number 8, your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman,

president of the National Center for Health Research. Our center is a non-profit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My perspective is as a scientist trained in epidemiology and public health and as a former faculty member and researcher at Vassar, Yale, and Harvard. I've also worked at HHS. I'm a breast cancer survivor, and I've worked with many breast cancer patients.

Chemo and surgery work for many triple-negative breast cancer patients, but we need additional treatment options that are safe and effective. I'll focus first on whether there's evidence that immune checkpoint inhibitors are effective for TNBC. I agree with FDA scientists that there's still uncertainty about that based on the results from several clinical trials, which as the FDA points out failed to meet an overall survival endpoint; and in one study, survival was better for the control group.

The research question is, is Keytruda effective as a neoadjuvant with chemotherapy followed by surgery; is it effective as an adjuvant after surgery; or both?

My second major focus is going to be on pCR data. Our analysis agrees with FDA's that there was only a 7.5 percent improvement in pCR, which we agree may not be clinically meaningful even if it's statistically significant. It's impossible to know how this slight improvement would affect overall survival; and even if it does, how much neoadjuvant and adjuvant use each might contribute to any benefit.

On event-free survival, we agree with FDA that it's not statistically significant, not clinically meaningful, and did not show a stable trend, and that's why this study should be continued to determine any benefits, and for whom.

FDA reviewers concluded that data on overall survival are, quote, "too immature to provide a conclusive interpretation regarding the difference in overall survival between treatment arms," and we

agree. And what about safety? There were 96 deaths, which FDA points out is less than one-third needed for the final analysis. So the overall survival estimate may be unreliable and the treatment effect size reported is uncertain.

I'm glad that KEYNOTE-522 included patient-reported outcomes but, unfortunately, it was not designed to compare differences in those outcomes, in symptoms, in side effects, or health-related quality of life, and patient-reported endpoints were not prospectively identified or statistically tested. Those patient-reported assessments should have been more frequent, both for the neoadjuvant and the adjuvant treatments.

Many high-risk, early-stage TNBC patients will be cured with standard therapy, as FDA has pointed out. So what's the risk versus benefit shown in this study? The benefits are unclear, but the risks are clear. There are toxicities that can be irreversible and some that would require lifelong medication in patients that have been

cured of their breast cancer.

The sponsor counted two deaths due to immune-mediated adverse events, and the FDA counted four. There were many other serious adverse events. Forty-three percent of all immune-mediated adverse events were in the Keytruda patients compared to 22 percent in placebo; and of those that were higher grade adverse events, 15 percent were in the Keytruda patients versus 2 percent in placebo. Ten percent of the hospitalizations due to adverse events were in the experimental group versus 1 percent in the placebo group.

These adverse events were not resolved at the last assessment in the study for 19 percent of the Keytruda patients. Sixteen percent had initiated thyroid hormone replacement during the study just as an example of how serious these adverse events are.

In summary, the deaths are particularly concerning because these patients can be cured without Keytruda. All immune-mediated adverse events, including the worst ones, were increased in

those patients. As FDA has pointed out, some of these may be severe or lifelong, and the adjuvant treatment has fewer adverse events but has not demonstrated efficacy at all. So it may add risk without any benefit.

The FDA conclusions were very clear and our analysis agrees with them. Neoadjuvant use, quote, "confers only a small absolute improvement in pCR rate of questionable clinical meaningfulness," unquote.

Event-free survival and overall survival are, quote, "immature and unreliable," unquote. KEYNOTE-522 does not currently support a role for adjuvant use and, quote, "supportive data of clinical benefit are lacking," unquote.

The toxicity from the drug may be, quote "severe, irreversible, and/or require lifelong medication in potentially curable and otherwise healthy patients."

In conclusion, we do patients no favors to approve a treatment that is not proven to benefit them and is proven to cause harm for a substantial

percentage of patients. I know from my own experience, we all want hope, but hope doesn't save lives, and that's why the FDA has to rely on the science.

Thank you very much for the opportunity to speak today.

Clarifying Questions to Presenters (continued)

DR. HOFFMAN: The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

We will now take remaining clarifying questions for all the presenters thus far. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked your question. And please remember to state your name for the record before you speak and direct your questions to a specific presenter if you can.

If you wish for a specific slide to be displayed, please let us know the slide number if possible. And as a gentle reminder, it would be helpful to acknowledge the end of your question

with a thank you and end of your follow-up question with, "That's all for my questions," so we can move on to the next panel member.

We're going to go in the order. There were a number of members of the committee who had their hands up before we had the break, and I want to be sure that each one gets their chance before we might go back to some who've already spoken.

I had a question for the applicant, probably Dr. Karantza. On CE-7 slide, I was wondering if you could put that up for a moment. And in particular, it related to the fact that a smaller percentage of patients on the pembrolizumab arm proceeded to adjuvant therapy than on the placebo arm; at least that was what I took from that slide, CE-7 --

DR. GOODMAN: Can we get CE-7, please?

DR. HOFFMAN: -- near the bottom there.

DR. GOODMAN: Vicki Goodman, vice president, clinical research. You're referring to the 75 percent who started adjuvant therapy on the pembrolizumab arm compared to the nearly 85 percent

on the placebo arm. Is that correct?

DR. HOFFMAN: Yes.

DR. GOODMAN: And your question?

DR. HOFFMAN: What was the difference or was this because of dropout, or why?

DR. GOODMAN: Right. So I will ask Dr. Karantza to speak specifically to the reasons why patients did not proceed on to adjuvant therapy. I will note that the patients who completed neoadjuvant chemotherapy was quite similar on the two arms, and Dr. Karantza can share those data as well.

DR. KARANTZA: Yes. Thank you.

So as you mentioned, about 25 percent of patients in the pembro group and 15 percent in the control group did not receive adjuvant therapy. The most common reason why patients did not get adjuvant therapy was discontinuation of pembro/placebo due to toxicity in the neoadjuvant phase. That incidence was 14.3 percent in the pembro group compared to 4.9 percent in the control group.

Here is where we need to mention that the patients were discontinued pembro/placebo due to an adverse event. They could not get it in the adjuvant phase. Discontinuation of pembro/placebo did not mean discontinuation of chemotherapy, so actually, the exposure to chemotherapy was very similar in both arms.

Furthermore, there were a few more reasons why patients did not get adjuvant therapy, and those included disease progression before surgery. There were a few patients that had a disease recurrence after surgery before starting adjuvant treatment, and then there were a few patients with withdrawal of consent or physician decision.

DR. GOODMAN: Thank you, Dr. Karantza.

DR. HOFFMAN: Okay. Thank you. That's all for my question.

I think next, Dr. Halabi had a question.

DR. HALABI: Thank you. Dr. Hoffman.

This is Susan Halabi. I have a couple of questions, really, more a clarification for the applicant, and then another question for the FDA.

Following up on the definition of EFS, since it wasn't consistently defined between the sponsor and the FDA, for the next interim analysis it is expected that there will be 200 events. In essence, the applicant is waiting for 47 more events to occur for the next interim analysis.

Assuming this occurs -- and I know you will probably not have a look at the OS. But one thing that I was a little bit concerned was the association between pCR and EFS. In all the studies that were presented, I assume they included the positive margin patients. Is that correct? Specifically I'm referring to slides CU-7.

If you also bring up the slide that did the sensitivity analysis with a hazard ratio of 0.68, please up, because I had some questions regarding that.

DR. GOODMAN: Dr. Halabi, maybe I can address the first part of your question, and in particular speak about the relationship between pathologic complete response and event-free survival. We did, as you note, use a slightly

different definition of EFS than some other trials have used with respect to the positive margins. As you've seen, that has had a minor impact on event-free survival in a sensitivity analysis.

But I think the point you're raising about the relationship between pathologic complete response and EFS is a really important one. We are fortunate to have Dr. Don Berry with us today, and the relationship between the magnitude of improvement in pCR and EFS in subtypes of early breast cancer, including TNBC, was modeled and published by Dr. Barry and Dr. Hudis, based on FDA's meta-analysis of neoadjuvant breast cancer trials.

What we're seeing is that the magnitude of EFS improvement in our interim data exceeds what would be expected based on this modeling, which for TNBC was based on chemotherapy trials, as you've noted. So I'd like to ask Dr. Berry perhaps to speak to that modeling work and contrast it to what we're seeing in KEYNOTE-522.

DR. BERRY: Thank you, Dr. Goodman.

This is Don Berry, consultant to Merck. Slide up, please. The figure on this slide is modified from the article that Dr. Goodman mentioned and Cliff Hudis and I published in JAMA 2015.

The article deals with the role of the Cortazar FDA meta-analysis in designing and interpreting results of clinical trials that are consistent with the FDA's neoadjuvant breast cancer guidance.

The horizontal axis in this figure is the increment and pCR rate for an experimental therapy over control. The vertical axis is the corresponding EFS hazard ratio for the experimental therapy against control. The solid black and orange curves show the expected hazard ratio, assuming that an increment in pCR rate moves the corresponding proportion of patients from the no pCR curve to the pCR curve in the FDA meta-analysis. So black is TNBC; orange is HER2-positive disease.

The point of the article is to show that the

meta-analysis is highly predictive of a controversial conclusion from two trials in HER2-positive breast cancer, one neoadjuvant and the other adjuvant. NeoALTTO had shown an apparent substantial 20 percent increment in pCR rate. We're adding lapatinib to standard HER2 therapy, while ALTTO had shown a seemingly modest EFS hazard ratio of 0.84 for the same therapy.

As shown in the figure, the meta-analysis predicted a hazard ratio of 0.83, so essentially the same, thus arguing that the meta-analysis was completely consistent with the result of both trials.

Similarly, as the figure shows, in TNBC the addition of carboplatin is standard neoadjuvant therapy, and CALGB 40603 showed a 14 percent improvement in pCR rate and an EFS hazard ratio of 0.84, which is exactly what the meta-analysis in this molecular subtype predicted.

However, as Hudis and I wrote at the time, quote, "A new therapy's effect may not translate to EFS in the same way as do the collective

chemotherapies in the FDA meta-analysis. The hazard ratio for a given pCR improvement might be larger or smaller than shown in the figure.

"Including interim analyses of EFS by pCR within treatment arm of a phase 3 trial can mitigate this uncertainty by tailoring the trial sample size to the accumulating evidence. Updating the meta-analysis using results that apply for the actual treatments and circumstances of the trial can be highly valuable," so end quote.

What does this mean for pembro in 522? The open circle shows a modest 7.5 percent improvement in pCR rate. The predicted EFS hazard ratio is a very modest 0.9, far from the 0.65 observed in IA3 and requiring a trial much larger than KEYNOTE-522 to be powered to show an EFS benefit. Indeed, as shown in the figure, 0.9 is not even within the IA3 95 percent confidence interval.

Pembrolizumab has an apparent beyond-pCR impact on EFS. As Dr. Rugo suggested, perhaps a relationship between pCR and EFS is different in IO than for chemotherapy, or the year-long treatment

with pembro in the trial may be delivering an additional boost for patients whether or not they had achieved the pCR. But for whatever reason, the FDA meta-analysis does not explain the results of KEYNOTE-522.

In any case, the results of KEYNOTE-522 are still in complete accord with the FDA's guidance. Quoting from the guidance, "A single-trial model," as mentioned by Dr. Shah, "may enable a single, well-controlled, randomized trial if adequately powered and sufficiently compelling results would serve as the basis for both accelerated and traditional approval," end quote.

The predictive analysis, based on the interim EFS results at IA3, make clear that KEYNOTE-522 is adequately powered, having an overall predictive power of 97.6 percent. And I'd be happy to explain this calculation to repair some of the misinterpretations of our calculation that was represented by the FDA's presentation. So thank you.

DR. GOODMAN: Thank you, Dr. Berry.

I'll re-emphasize again, we don't know what magnitude of pCR benefit will lead to a benefit in a clinical endpoint such as EFS, in particular for immunotherapy. However, what we're seeing here is, based on the early data we have for EFS, a benefit which appears to exceed that, that we would expect from pCR, based on the FDA's meta-analysis, which is consistent with the mechanism of action of immunotherapy, where frequently the effects on long-term outcomes are not captured in response data. Thank you.

DR. HALABI: Thank you. I still have my next question, which is, again, the hazard ratio based on 168 [indiscernible] EFS. So if we look at the hazard ratio, that estimate was 0.68 with a 95 percent confidence interval of 0.5 to 0.92. And perhaps Dr. Berry may be able to answer that in the calculation of the predictive probability.

Did you take into consideration a potential hazard ratio of 0.92, and what was that? That was the one question.

Then the follow-up question regarding the

meta-analysis had to do with the definition of EFS. Did you in the analysis include patients with positive margin, and what was that very small component of your endpoint? That is similar to what's observed in KEYNOTE-522 of, I believe, 1.34 percent. Thank you.

DR. GOODMAN: Dr. Berry, would you like to address that follow-up question?

DR. BERRY: Yes, there are two parts. One part is the 0.68 that is excluding positive margins as an event, and Dr. Karantza's presentation demonstrated that these are -- I hesitate to use the word -- a surrogate for later events, at least in many of the cases.

We looked at that as a sensitivity analysis, yes. It doesn't change much. I mean, the 0.65 changes to 0.68. The number of events, and therefore the precision associated with the estimate for the 0.68, is somewhat less than the 0.65. It changes the predictive probability somewhat, but qualitatively speaking, it's very similar.

To address the 0.92, it relates to this issue of what the FDA calls the applicant's model and what is the real applicant's model.

If I can have slide ST-7, please? Slide up, please. This, Dr. Halabi, shows the current likelihood for the IA3, for the EFS hazard ratio, and that's the thing on the left. The panel on the right shows the predictive power over time.

This is a Bayesian concept. It uses the likelihood ratio as the posterior distribution. The FDA suggested something about the prior distribution. Well, the prior distribution is flat. It's open-minded. It's not informative. The posterior distribution in the Bayesian approach is based exclusively on the data in the trial.

The hazard ratio that it shows, this is a histogram hazard ratio that it shows. There's a 0.9 down at the bottom. There's 0.92. There's somewhat less likelihood associated with the 0.92 than 0.9.

What the FDA did, and called it the applicant's model, is looked at the 0.4 -- I

believe. They didn't say explicitly what they did. They looked at the 0.4, the 0.1, and gave a range. That's not what the Bayesian approach is. The Bayesian approach is an average of the power, where the weights in the average are the current likelihood. So the things on the right show that for IA4, that number is 0.73; so 73 percent probability of statistical significance at IA4, given the number of events that you mentioned.

This is within the FDA's range, actually. The reason it's within the FDA's range is what the FDA did in their calculation was to assume 0.65 and 0.8 and considered two values. One was 0.62 for the predictive probability -- that's the 0.8 shown on the left-hand panel with that red dashed line -- and 0.65, which is the point estimate of the hazard ratio, which is the most likely estimate; and they came up with a 0.78.

So that range as shown for IA4 is to indicate they hesitated to look at the later endpoints because of the lack of reliability. And indeed, when you add more time to what you're

predicting, that time leads to greater uncertainty. On the other hand, when you go from IA4 to IA5, there's greater precision in the estimate in IA5 and in IA6 because we're getting more and more information. So these are cumulative predictive powers.

As you get up to the final analysis, the probability that you see at least one of these that is a positive conclusion is 0.976, so a very high probability; and as I indicated earlier, adequately powered.

So the 0.92, if you assume 0.92, that would be beyond the pale, and it's not very likely that KEYNOTE-522 is going to show statistical significance if in fact the truth is 0.92. But that has extremely low probability in view of the data that we've seen in IA3. And indeed, the confidence interval -- and this is using the 0.65 that is with the positive margins -- goes from 0.48 up 0.88 with the -- I've forgotten the number now -- 0.68 that's wider and somewhat shifted to the right, and includes the 0.92.

So back to the second point, the issue of the 0.68 versus the 0.65, yes, a difference; not a very important difference. Thank you.

DR. GOODMAN: Thanks, Dr. Berry.

So when we look at the totality of the evidence with a favorable effect on pathologic CR rate as well as the interim EFS data, which you've seen, we believe that the totality of the evidence here, along with what we've shown in the metastatic setting in KEYNOTE-355, are reasonably likely to predict clinical benefit. Therefore, we are requesting accelerated approval on the basis of the -- [inaudible – audio gap].

DR. HALABI: Thank you. Those questions were addressed. The final question I had is really for the FDA.

In the event this was not approved for accelerated approval, would the sponsor be able to come back for another application for accelerated approval if there is a statistically significant EFS with 405 EFS events?

DR. AMIRI-KORDESTANI: Hi. Can you hear me?

This is Laleh Amiri from FDA.

DR. HOFFMAN: Yes.

DR. AMIRI-KORDESTANI: To address your question, yes, the sponsor may submit future applications for regular approval or accelerated approval when they have further data, which basically you stated from the next interim analyses.

I also wanted to clarify and add a comment about the prior question that you raised with the applicant. It hasn't been FDA's practice to approve a drug based on likelihood or modeling a future statistical significance. So our thinking is that we need further follow-up, and that's the only reliable way that we can characterize event-free survival for this patient population.

I'd like actually to ask our statistical reviewer, Dr. Amatya, to add a comment.

DR. AMATYA: Yes. I hope you can hear me.

DR. AMIRI-KORDESTANI: Yes.

DR. AMATYA: Okay.

Well, what Dr. Berry said was supposedly the

applicant's model actually is the applicant's model. The applicant provided us with the predictive probability model and programming code used to generate the results, as well as a potential distribution for hazard ratio.

Although we computed the range using the same model and the same programming code as the applicant, the range that we provided under the applicant's model is based on predictive probability calculated from all the 8 scenarios that were included in the programming code; whereas the range that the applicant has provided is based on 2 of 8 scenarios.

As stated earlier in the presentation, these predictive probability models are highly sensitive, although it was presented as very specific. But they are very variable based on the modeling assumption. And our view is that it should not replace the continued follow-up of EFS needed to adequately characterize, again, a clinical benefit of pembrolizumab on EFS.

I also will add that the applicant's data

monitoring committee has also recommended this study to be continued without change, and that efficacy has not been demonstrated in interim analysis 3.

DR. HOFFMAN: Thank you.

We are running low on time, but I want to be sure that Dr. Hayes, and Dr. Wolff, and Dr. Kraus can ask their questions hopefully succinctly.

Dr. Hayes?

DR. HAYES: Yes. Thank you very much. I very much appreciate all the comments by both the applicant and the FDA, and especially the public comments.

I have three questions. The first of those -- and it just sort of came out in the last answer -- is, in the briefing document that we received, it does mention that there was a discussion with the DSMC, but it doesn't provide us information as to whether the DSMC actually agreed with moving forward with this submission.

So I guess this is a question to the applicant. Was the DMC in agreement with your

current strategy?

DR. GOODMAN: So as you've heard, the DMC met regularly, and at interim analysis 3, as EFS had not yet met statistical significance, asked for the trial to continue. I will ask Dr. Karantza to address specifics of what was discussed with the DMC with respect to submission plans.

DR. KARANTZA: This is Valia Karantza. I'm the clinical lead for the breast program at Merck. In regards to the DMC's recommendation, that was a recommendation that the study should continue. So of course we took that recommendation, and the sponsor remained blinded at that point to the IA3 results.

In regards to the filing, the applicant made the decision to file. Again, the DMC is an advisory committee. We did notify the DMC that we were submitting an application. We did not get any objection.

DR. HAYES: So I just want to be sure I understand what you just said. You had no objections from the DMC for currently unblinding

and submitting these data.

Is that true?

DR. KARANTZA: No, no, no. No. Okay. I think there is a big misunderstanding here. The IA3 data, the sponsor was unblinded only to IA2 EFS data. The sponsor was blinded to IA3 data. The DMC only recommended that we continue. Nobody in the sponsor was communicated the specific results. So we applied based on the interim analysis 2 EFS and interim analysis 1 path CR.

During the process of our application, the FDA asked for the IA3 results, at which time point only an executive committee within Merck, actually in a blinded fashion, provided the data to FDA. The sponsor's team for the application was still blinded. And only upon a consultation with FDA, was it suggested that it would be good for the sponsor to actually be unblinded so that the IA3 data could be discussed at this meeting. So that is the only way we got unblinded.

DR. HAYES: And does --

(Crosstalk.)

DR. KARANTZA: Yes?

DR. HAYES: Does the DMC have concerns, ethical concerns, about if this were to get accelerated approval, that there would be huge interest in unblinding at a patient level so that patients could decide if they do or do not wish to take the drug?

DR. KARANTZA: There was no such concern conveyed to us.

If I may make one comment, the IA2 results were already public with a hazard ratio of 0.63. We do follow closely any unblinding request. The only unblinding that is permitted, unless it's an emergency unblinding, is for documented disease recurrence with a biopsy and/or imaging scans, and we have not seen an increase in unblinding since the IA2 results became public.

DR. HAYES: But public --

(Crosstalk.)

DR. GOODMAN: Dr. Hayes --

DR. HAYES: -- FDA approval.

Yes, please?

DR. GOODMAN: Dr. Hayes, I will also note that all patients are off of treatment at this point, so the sponsor did take multiple steps, as you've heard from Dr. Karantza, to keep the study team blinded, and we were unblinded to IA3 late. However, all patients have been off of study treatment now for approximately one year.

DR. HAYES: Okay. Thank you.

My second question I guess is directed to Dr. Rugo. She gave a compelling testimony that delay would result in many patients suffering an event -- I can't remember how many she said -- that would not have had to. We've also heard, I think, that the next assessment will come after 47 more events. I presume that's a few months into 2021. That was implied.

So my real question is, how many patients during that period of time, and what percentage of the overall group of patients in the United States that might have benefited, would suffer distant recurrence, not any event -- because events, as we've heard, are both positive margins but also new

primaries and death of any cause -- versus the 1 percent expected mortality rate with this drug in all trials, as far as I can see? It's about 0.75 to 1 percent mortality rate.

It seems to me that the 6-month delay or so it would take to see IA4 would just about be a wash in terms of the number of distant metastases that are prevented and the number of potential fatal adverse events.

Dr. Rugo, do you want to respond to that?

DR. GOODMAN: Before I turn this over to Dr. Rugo, which I'll do in a moment, just a couple of clarifying comments.

I think one is that the interim analysis is calendar driven and not event driven, and we're expecting the data would be available in the third quarter of this year.

The second is coming back to the question on deaths, what we were speaking about earlier was the overall deaths due to an AE, whereas the treatment-related deaths due to an AE was approximately 0.5 percent. Again, not that we

should be comfortable with any deaths, however, I think that does help put their benefit-risk in perspective.

Perhaps now I'll turn it over to Dr. Rugo to talk a little bit more about additional recurrences -- I'm sorry, with one more comment, which is that while IA4 has a reasonable likelihood of demonstrating a clinically meaningful and statistically significant benefit, of course that's not a guarantee, and we may be waiting substantially longer than that.

So with that, I'll turn it over to Dr. Rugo.

DR. RUGO: Thanks. Certainly, I'd welcome any comments from Don Berry or others at the end of my comment.

It's a great question. I think the concern that I have as a clinician is the plateau that we see, which means that there are continued recurrences, but the rate slows down. So it could take us a very long time to see the benefit we're looking for as that rate slows down, based on our historical data over time. But you need a certain

number of events in order to see the difference you're seeing, and there's a time-driven approach as well that was just described.

In terms of balancing this against the toxicity, this is a critical issue. We're always doing a risk-versus-benefit analysis and thinking about adding new drugs. As I mentioned earlier, I feel like the patients who are at the highest risk also have the highest risk of dying early. So if we could prevent recurrences of the triple-negative disease, that's of course great; everybody wants that. But we need to balance it, as you've put forth very nicely, against the known risks.

In this trial, which was done in many, many sites where people really didn't have a lot of experience using immunotherapy anywhere, I think that it's important to look at some of the toxicities and how they could be prevented by simply knowledge and experience, and providing educational materials.

So I guess in my thinking of this, actually when you become more familiar with understanding

immune toxicities and intervening early, we could really significantly reduce the potential issues that have been seen across different trials and across different malignancies using these checkpoints inhibitors.

DR. HAYES: Well, I don't want to belabor this further. I'd like to ask my third question, and this is directed towards Dr. Berry, who gave us an extraordinary lesson in Bayesian statistics. But it seems to me that there is a cohort effect that we're ignoring.

For example, Dr. Rugo just mentioned the plateau, but the plateau has occurred after the median follow-up, which looks to be about 23 to 27 months. So you've got half of those patients who are still relapsing, who are coming into that median follow-up time.

Don, this really is asking you a question, because the slide you showed for predictive power, you're assuming that the cohort coming into this is the same as the cohort going out. But as you know -- you taught me frankly -- that's not always

the case.

Furthermore, it seems to me the slide you showed was the predictive power for predicting that something was going to happen and that IA4 was better than IA3. I agree, but that doesn't mean it's predicting for a positive outcome, does it? Doesn't that just mean increasingly gaining power to protect what's going to happen in the long run until you get to the final analysis?

So unless I'm mistaken, you showed the predictive power was going up-up, which I agree, but that's not predictive power for a positive outcome; it's predictive power for what the outcome really is, or did I misunderstand that? It seems to me that could go either way, for a positive or a negative effect from the recurrence of about 75 percent positive prediction.

Am I misunderstanding, Don?

DR. GOODMAN: Dr. Berry?

(No response.)

DR. HAYES: Dr. Berry?

(No response.)

DR. GOODMAN: Don?

(No response.)

DR. HAYES: Well, that's unfortunate because I want to be sure I understood that set of curves he just showed, and I don't think I do. And it's pretty critical to what Dr. Rugo just said in regards to anticipating whether the benefits outweigh the risks here.

DR. GOODMAN: Dr. Hayes, just give us a moment and let me see if we can get through to Dr. Berry.

DR. HAYES: Thanks.

DR. HOFFMAN: In the meantime, I think, Dr. Pazdur, did you want to make a comment before we move on?

DR. PAZDUR: Yes. Hi. This is Rick Pazdur -- done information on this, and I think it's --

DR. HOFFMAN: You're breaking up.

DR. PAZDUR: -- [inaudible – audio gap] need to understand -- accelerated approval, and regular approval, or conventional approval.

For both of these approvals, whether one talks about accelerated approval or a conventional approval, one needs what is known as substantial evidence, and substantial evidence is a statistical persuasive effect on an endpoint.

This is not about a guessing game of whether the drug works or whether a model shows something. This is basically an effect on an endpoint that is reasonably likely to predict a clinical benefit, and on a clinically meaningful endpoint of a sufficient magnitude here.

So this is not about guessing whether something would happen, so to speak. It has to be demonstrated, especially if you're talking about an adjuvant therapy here, where we don't really have mature data to make that decision.

I just want to make people understand, it's really the basis of an endpoint that one is looking at, either an early clinical endpoint or a surrogate endpoint, but the effects on those endpoints should be statistically persuasive. And I think that's very important for the committee to

understand our rationale and our reasoning on this, and our discussions on this from the FDA perspective.

DR. HAYES: Dr. Pazdur, this is Dan Hayes again. I think your comments are supporting my concern that we can't really predict what's going to happen without actually seeing the real data. We can make a --

DR. PAZDUR: Correct.

DR. HAYES: --logical guess. Just like predicting a football game, one team looks better than the other, but that's why you play the game. I think that's what you're saying.

DR. PAZDUR: For example, let's take this to a metastatic disease setting. We won't accept somebody coming in with interim analysis, basically, at any time point, just saying we're modeling this to determine whether an effect is there, so to speak.

We need to see that effect and whether it is an effect on EFS or an effect on overall survival. Substantial evidence needs to exist. We can't be

put in a predicament of potentially approving a placebo here or something of very, very marginal benefit, especially considering the toxicity of this drug and the long duration of use of this drug.

DR. HAYES: If Dr. Berry comes on, I think what Dr. Pazdur just told me is that although it's more likely to be a positive than a negative study, it could still go either way. And that's why we need a longer follow-up and more events to determine, especially given the potential 1 percent or so, 0.5 to 1 percent, mortality rate.

Richard, I'm putting words in your mouth, but is that what you just said?

DR. PAZDUR: In a sense, yes. We have to have substantial evidence to determine whether there is an effect on an endpoint.

DR. HOFFMAN: Okay. Moving on, Dr. Wolff, I think you had a question earlier.

DR. WOLFF: Thank you very much. The hour is late, and my question is more a follow-up to the comments. And I'm happy to yield time so that I

could make them during the discussion before the time we vote. So I can yield back to you.

DR. HOFFMAN: Okay.

Dr. Kraus?

DR. KRAUS: Yes. Albert Kraus, industry representative. Actually, I will do the similar because Dr. Halabi kind of brought out the whole discussion of pCR relationships, et cetera, so I'll not ask the question again. Thank you.

DR. HOFFMAN: Okay. I think I've covered everyone who has their hand up for a question.

Am I right?

(No response.).

DR. HOFFMAN: Okay. I think I'll ask those of you who have completed your questions to put your hand down, please, and we'll now move on to today's question.

I'm sorry. We're going to turn our attention now to address the task at hand, which is the careful consideration of the data before the committee, as well as the public comments. We'll proceed with questions to the committee and panel

discussions. And I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I think it's now up to the committee to discuss these things, and maybe I should let Dr. Wolff or Dr. Kraus move on if they were holding their comments.

DR. BERRY: Don Berry is on.

DR. GOODMAN: Dr. Hoffman, I think Don is back – yes -- if you'd like him to take that earlier question.

DR. HOFFMAN: Okay. Why don't we finish up with that, with Dr. Hayes' question.

DR. GOODMAN: Perhaps, Dr. Hayes, if you could repeat the question.

DR. CHEN: Sorry, everyone --

DR. BERRY: Hello?

Dr. Hayes, could he ask his question again?

DR. HOFFMAN: You know, I think maybe we probably covered that sufficiently.

Dr. Hayes, do you feel that we have?

DR. HAYES: I personally feel that we have, unless the applicant feels that I've misunderstood and Dr. Pazdur's comments are also a misunderstanding. But I believe I've received the information I need.

DR. HOFFMAN: Okay. So let's move on to the committee's discussion, then, at this point.

Dr. Wolff, would you like to make a comment?

DR. WOLFF: So, I do, and this may be the only time that I actually need to speak; there are many of us. Mine is a comment but also qualified comments to observations made by Dr. Rugo and Dr. O'Shaughnessy.

I think this has been incredibly informational to me. I want to thank Merck advisors and the FDA for all of this. I also am very touched, honestly, by all who spoke during the open public hearing, and my deep appreciation for all of you who spoke and who participated in the clinical trials that allow the data we have so that we can continue to improve outcomes for the next

generation of patients and their loved ones, and especially those of you who participated in KEYNOTE-522.

I say this because we're all trying to have what I call the Goldilocks approach. We don't want to do too much, we don't want to do too little, and we want to help patients while we minimize harm from our best intentions.

I say this with the perspective of being both a clinical researcher, as I am chair of the NCI-funded ECOG-ACRIN Breast Cancer Committee, but I'm also a breast cancer doctor, and I see patients in clinic two full days a week. So I have individual discussions and individual decisions very often.

I'm also past chair of ASCO's Clinical Practice Guidelines Committee. Dr. O'Shaughnessy earlier mentioned the recent ASCO guidelines for neoadjuvant chemo, endocrine therapy, and target therapy for breast cancer. And for those of you who want to read more about this, the PubMed id is 33507815. And it's important to say the guidelines

were developed based on evidence, and they are informed by clinical experience, especially when evidence is lacking.

So here we're dealing with neoadjuvant therapy followed by adjuvant therapy. Neoadjuvant treatment was originally developed to manage locally advanced breast cancer, and then a substantial interest developed to help both officially use pathologic response, or pCR, as the intermediate endpoint, the so-called surrogate marker, to help identify treatments that would most likely translate into improved survival.

Therefore, clinical trials would then propose to allow testing of drugs that phase on path response could then graduate to continuing for larger studies now powered to test survival, and Dr. Don Berry himself has been involved with many of these studies.

This led to two schools of thoughts: one, that reaching a path response, pCR, is the main goal; a second one, that a path response can be used as a functional biomarker to help us modulate

or optimize subsequent treatments so that you could start with a little bit less therapy first, and then use the initial response such as surgical response to help you make decisions about escalation or de-escalation.

The guideline itself, which just came out, published a couple of days ago, in one of the recommendations, 1.3, neoadjuvant therapy should be offered to patients with high-risk, HER2-positive, or triple-negative disease so that the finding of residual disease would guide recommendations.

I think we are in a situation where we have data in HER2-positive disease with cathren [indiscernible], but also we have data from CREATE-X and the other Chinese studies recently published in triple-negative disease, and it's actually -- I didn't recognize it at first because it was called KEYNOTE-242, which is a confirmatory study for the one we are reviewing today. I actually know that study as SWOG 1418, which is a post-neoadjuvant randomization to pembrolizumab versus observation in patients who don't reach a pathologic complete

response.

I think this shows us how we have learned today to use the neoadjuvant setting not to try to achieve pCR at any cost with more therapies, but perhaps to use its information to guide what we do afterwards.

The ASCO committee also mentioned about carboplatin, and this is something Dr. O'Shaughnessy touched on. It says that carboplatin may be offered, and ASCO instruction is to use -- may, must, or should, and in this case it's "may", may be offered as a neoadjuvant, follow the neoadjuvant's regimen, and the decision to offer carboplatin should take into account the balance of potential benefits and harms. And I wonder whether this is where we are today with checkpoint inhibitors.

Finally, a recommendation from the committee, which was based on the publication last year in the New England Journal of Medicine of the first results of the KEYNOTE-522 study, is that there is insufficient evidence to recommend

routinely adding the immune checkpoint inhibitors to neoadjuvant chemotherapy.

I would say in response to Dr. Rugo and agreeing with what Dr. Ellis mentioned, I think we need to be careful not to discount published externally reviewed data from randomized trials, such as the data from the two Asian studies that they have cited, and replace them with our individual, anecdotal clinical experience of taking care of patients in the U.S. with these drugs.

We have to remember that even if we want to discount those experiences, here today we are being asked to make recommendations about this new drug in breast cancer based on incomplete data, immature data, and information from interim analysis number 3 that allows the DMC to recommend continuation of the trial, and may be addressing Dr. Hayes' concerns.

My understanding of how these things work and perhaps what's happened here, I don't think the DMC would have a role in opining on the decision by the sponsor to ultimately submit an application or

not.

So I think the decision to give an accelerated approval to pembrolizumab a number of years ago was a difficult one, but we have to remember that in that case, two therapies have very established track records in advanced disease with trastuzumab and pertuzumab with survival data and also in the adjuvant setting with trastuzumab.

I think the question for many of us today is whether the available data with checkpoint inhibitors, and specifically pembrolizumab -- is there two?

I recognize that most of these principles that I'm discussing are based on what we think we know about chemotherapy and about HER2 antibody therapy, which in some ways is another form of immunotherapy. But the reality, though, is that we really don't know, to date, how to best use checkpoint inhibitors in breast cancer so that one day we can observe the astounding results that we have seen with this class of drugs, and pembrolizumab itself, in other solid tumors that,

thus far, seem to have eluded us in breast cancer.

And finally, I think we need to be cautious and not minimize the toxicities that could be life-altering for patients with early-stage breast cancer that could potentially be cured with standard therapy alone. And I am not at all minimizing what a horrible disease this is, especially when it comes back.

Those are my comments. Thank you.

DR. HOFFMAN: Dr. Kraus, let's give you an opportunity.

DR. KRAUS: Okay. Thank you. Albert Kraus, industry representative.

Yes. It's very interesting, and I agree with all the comments about the varied input, and it's very helpful, and it's very productive, and it is a horrible disease. That's why we're here and talking about accelerated approval, I think, and hoping that we find more for patients.

The thing that strikes me is the design of the study in neoadjuvant and adjuvant phases, and the evaluation from Dr. Berry presenting the

predictivity of pCR, which would predict a lower effect, as I was understanding, if it was neoadjuvant therapy only. But the trial itself merged neoadjuvant and adjuvant therapy, and the data itself appears very promising at the interim 2 and 3; and from what I understand from FDA and the company, is likely to be positive. Whether it's two-thirds chance, a 75 percent chance, a 95 percent chance, depends on the assumptions, I guess.

The dilemma perhaps, what we need to discuss, is usually the surrogate endpoint is isolated and then thought to predict in a certain way on its own for approval. In this case, there's that strong contribution of a longer term adjuvant therapy that's not really captured in a pCR effect but may be contributing to hazard ratio in a trial that looks like it's going to be very productive and hopefully very positive in the end.

So the dilemma, I think in part that we're discussing, facing FDA is, in a way, it's leaning on a nonstatistical threshold crossing result,

though it looks very promising, from an interim analysis rather than a final statistical result, to kind of contribute to an accelerated approval decision, which indeed is a challenging one for the Food and Drug Administration because of the desire for substantial evidence.

That said, the patients have huge need, they're dying, they need more, and this probably helps. I'm not a physician. I work in the area of course, but I would say for this committee's discussion, it's very important to be balancing what's reasonably likely to result in an ultimate trial outcome of positivity and what's reasonably likely to be a benefit counterbalanced by the safety.

Because the question is, how many patients would be saved between now and when we wait, or if it's approved and if it doesn't work, and it has to be removed, what was the toxicity and the problems in deaths endured? And that's the balance, right?

So I'll stop there, but I'm just sharing my thoughts on issue in the discussion.

Questions to Committee and Discussion

DR. HOFFMAN: Okay. I may not have labeled it correctly, but we were still just now having discussion about clarifying issues.

We'll proceed with the questions to the committee and panel discussion. And I, again, would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

We're going to now move on to today's question, which is a voting question. Dr. She-Chia Chen will provide the instructions for the voting.

DR. CHEN: Thank you, Dr. Hoffman.

Question 1 is a voting question. The voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be

moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select a radio button that is a round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to.

Are there any questions about the voting

process before we begin?

DR. WOLFF: I apologize. This Dr. Wolff. I'm actually not sure if I'm seen the voting button. I apologize if I should.

(No audible response.)

DR. HOFFMAN: I'm sorry --

DR. CHEN: So now we are going to -- go ahead, Dr. Hoffman.

DR. HOFFMAN: Sorry. Go ahead.

Question 1. Should a regulatory decision on pembrolizumab in combination with multi-agent chemotherapy for neoadjuvant treatment, followed by pembrolizumab monotherapy for adjuvant treatment of high-risk, early-stage, triple-negative breast cancer, be deferred until further data are available from future analyses of KEYNOTE-522?

Are there any questions or comments about the wording of the question? And if not, we'll begin the vote.

(No response.)

DR. CHEN: We will now move voting members to the voting breakout room to vote only. There

will be no discussion in the voting breakout room.

(Voting.)

DR. CHEN: The voting has closed and is now complete. Once the vote result is displayed, I'll read the vote result into the record.

(Pause.)

DR. CHEN: Voting has closed and is now complete. The vote results are displayed. I'll read the vote totals into the record.

There are 10 yeses, zero no, and zero abstention. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state a reason why you voted as you did if you want to.

DR. HOFFMAN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. And as we said, you may also provide justification for your vote if you wish to.

We'll start with Mr. Mitchell.

MR. MITCHELL: Yes. Thank you, Dr. Hoffman.

I voted yes. My name is David Mitchell.

I'm the consumer representative. But I'm a patient with an incurable cancer, so I understand and respect deeply the wishes of the patients who spoke their wishes to have options, any options.

I'm fortunate with my cancer to have options, but options must be safe and effective. There has to be evidence that the benefits outweigh the risks. That is not the case in this application for accelerated approval today, and FDA should not be approving drugs based on modeling; only on actual data.

Although, especially for TNBC, time is of the essence, the FDA should look at the data coming later this year and ensure that this treatment will be an option that helps patients rather than hurts them.

DR. HOFFMAN: Okay. Thank you.

Dr. Portis?

(No response.)

DR. HOFFMAN: You can unmute yourself.

DR. COMPAGNI PORTIS: Oh. Can you hear me now?

DR. HOFFMAN: Yes.

DR. COMPAGNI PORTIS: This is Dr. Natalie Compagni Portis, and I voted yes. I'd like to thank the panel, and FDA, and our sponsors for a really robust discussion. And I thank you, Dr. Pazdur, for saying that we need to make decisions based not on guessing or hoping.

As the patient representative and someone who was diagnosed with breast cancer at 35 and who works with people with cancer every day, I know there's a clear unmet need, especially for younger women and African American women, and we absolutely need better and more effective options. And there are. There are very compelling reasons to wait, and I'm a little baffled by why the rush here, despite FDA saying let's wait for the complete data.

We really have a responsibility to patients to not prematurely offer treatment, and therefore hope, when we don't have solid evidence and benefit, and especially when we don't have evidence of overall survival benefits. These are patients

that are already receiving a significant amount of treatment that comes with long-term significant side effects and great impact on quality of life, and they're already dealing with toxicities from the existing treatments.

I think we often confuse our patients with regard to the relevance of PFS, and EFS, and in this case pCR, and it's vital that without any evidence of improved quality of life and with the known lifelong serious risks here, and without that evidence of overall survival, we really need to wait until we have complete data. Thank you so much.

DR. HOFFMAN: Okay. Thank you.

Dr. Armstrong?

DR. ARMSTRONG: Thank you. This is Deb Armstrong. I will keep it short. I voted yes. I hope this is a positive study, but I think that at this point in time it's premature to start treating patients with this therapy. Even under the intense scrutiny of a clinical trial, almost 1 percent of patients who were treated with this died as a

result of this treatment, and in the general community, that rate of -- [inaudible – audio gap] would likely be higher.

There is not another clear scenario with triple-negative breast cancer, where in this same population there is a clear benefit in terms of survival for the addition of pembrolizumab. So I think the most prudent thing and the thing that's safest for our patients who clearly need new therapeutic options is to make sure that we're not giving them false hope or treating them with things that can hurt them more than it can help them. Thank you.

DR. HOFFMAN: Thank you.

Dr. Seidman?

DR. SEIDMAN: This is Dr. Andrew Seidman. I also voted yes. I was not very impressed with the increment in pCR rate, despite speculation that perhaps a modest pCR rate could still be associated with improved overall survival, perhaps due to the adjuvant component or some speculative unique biological effect, as was offered.

I do think the event-free survival data are immature, and I also do hope we see further separation, and convincing separation, of those curves later this year. Despite comments about the design, I don't have real significant concerns about the foundation of chemotherapy used, and hopefully there won't be great heterogeneity in the adjuvant use of capecitabine.

In terms of the data in metastatic disease that would support the application, I would describe it as modest at best. If the toxicity profile remains stable but the trial does ultimately show a significant event-free survival, I don't have any great concerns about the toxicity profile.

DR. HOFFMAN: Okay. Thank you.

This is Philip Hoffman. I voted yes for a few reasons. I actually do probably expect and hope that this trial does turn out to be positive with more mature data. I did find it of interest that when it was published after the first interim analysis, the difference between the pathologic CR

rates between the two arms was about 14 percent, which is quite remarkable, and that it's now down to 7 percent.

I think the notion that Dr. Zalani said at the beginning, which we think it is reasonably likely that this difference in path CR will lead to an improvement in event-free survival and overall survival, I'm sure that's accurate, but things do change as they mature. So the fact that we're seeing trends and signals toward improvement I think doesn't mean that it couldn't change with time.

I don't think we should underestimate the safety either, as Dr. Armstrong noted. I use a lot of immune checkpoint inhibitors in a different clinical setting, and although I've seen some spectacular clinical results, I've also had some patients who can't enjoy one day of their spectacular results because of significant toxicity, constant steroid use, and so on.

So sorry for my voice, but I voted yes.

Next, Dr. Hayes?

DR. HAYES: This is Dan Hayes. I voted yes for many of the same reasons. I was reassured, frankly, by Mr. Mitchell and Dr. Portis' comments as patients since I have not been a patient. I've just been a doctor taking care of patients with this disease.

I have also chaired several DSMCs, data safety monitoring committees, and our job is always to first protect the safety of the patients, and second, protect the integrity of the clinical trial. I think we owe it to the women who agreed to be part of this trial to make sure that the integrity of this science is maintained so that we have a good answer when we're done, and I'm not sure we do. I was not impressed that we're there yet.

Finally, as Dr. Armstrong mentioned, on a clinical trial, which is presumably some of the best and most careful physicians in our field, it was about a 1 percent mortality rate. And like everyone else, I've seen patients have great responses to these drugs. I've also had at least

one patient pass away from similar drugs.

So these are not benign drugs, and I hope, like everyone else, this will be a positive study, but I don't think we know that yet. Thank you.

DR. HOFFMAN: Thank you.

Dr. Lipkowitz?

DR. LIPKOWITZ: This is Stan Lipkowitz from NCI, and I voted yes. Just to begin, because I haven't spoken before, I want to thank all of the presenters from the applicant, the FDA, and also the public commentary on this drug.

As an oncologist who sees breast cancer patients, I have not had cancer, but I do feel the pain of all the patients of mine who passed away from this disease, so I do agree that we need better therapy for this disease. But like all of the speakers before me in the last few minutes, I feel that we need to have statistically significant EFS and/or OS data before we approve a drug, and that modeling is not sufficient for that.

I think we've heard repeatedly that the relationship between pCR and outcome is tenuous at

best. We don't fully understand that. And worse yet, in this case, there's adjuvant therapy between the pCR and the EFS events, so that we really don't have a good tie between the pCR result and what that likely means for the EFS.

So for the reasons of not having convincing or mature data for the event-free survival, and for the toxicity, as you've just heard, including fatalities, I really had to vote yes for this question. Over.

DR. HOFFMAN: Okay. Thank you.

Dr. Wolff?

DR. WOLFF: This is Antonio Wolff. I voted yes. As I said before, this is an incredibly tough vote, and I say this because we're dealing with people's lives. We have no right to take hope away from people. I think all of us, and the investigators, we are hoping that the study will be a positive trial at the end of the day, the decisions to launch the trial, the efforts involved, and all the patients that have participated. But at the same, we have an

obligation to temper and to measure our hope with the evidence so that we can provide the best advice we can to the best of our ability. And that is the reason why I voted yes.

DR. HOFFMAN: Thank you.

Dr. Halabi?

DR. HALABI: Yes, Dr. Hoffman. This is Susan Halabi. I want to also thank the presenters and the speakers for a very robust and vivid discussion today. Especially, I would like to thank the FDA for the consolidated briefing documents.

The reason why I voted yes is for several, that other speakers before me have mentioned. I think one of the most important in my mind was the association between EFS and pathological CR. In the meta-analysis that was performed by Cortazar, they did show that there is a relationship at the individual level but not at the trial level because the R-squared was very small.

With regard to interim analysis 4, I think that definitely with more events, it's very likely

that we're going to hit the boundary, but my concern is one can never underplay the role of chance. I think more importantly, as indicated in the presentation, the magnitude of benefit as measured by hazard ratio will probably tend to increase towards 1.

Then finally -- and I think this is really important, and I believe others speakers mentioned that -- the integrity of the trial is really important. It is important that we have mature follow-up, and this would not jeopardize the trial because, obviously, there is a huge and unmet need for patients. For all of us, we have vested interest to see positive results, and I hope it will be positive. Thank you.

DR. HOFFMAN: Thank you.

Dr. Ellis?

DR. ELLIS: Yes. I guess I have the last word, I suppose. I used the pembrolizumab standard and put this data in that context; and, obviously, I think we all agree that it was not as a compelling story as that.

I would just like to close that as a cancer survivor myself, I was deeply moved by the public session and the sad display of suffering that was observed there. I also would just like to comment on the failure of the predicted biomarker.

This is not a disease we understand well, and I think we need to go back to the drawing board, to some extent, and work hard on molecular profiling techniques that might get to a better place when we're working out how to place a drug like pertuzumab.

I too hope the next analyses produce a convincing result. I don't think we should approve drugs based on projections. We need solid evidence to prescribe drugs, and I'll leave it at that.

DR. HOFFMAN: If I can briefly summarize, I think it's clear that in the couple of years that I've been on the ODAC, this is the first time that I've encountered a voting question that basically said should we defer this as opposed to the yes or no, has the efficacy and safety been demonstrated; so yes or no, we should approve.

I think that many, if not most of us, believe that this trial may well turn out to be positive as time goes on with further analyses, as we see what the effect of the pathologic CR rate does in fact lead to. But I think there certainly is consensus among the committee that that hasn't yet been demonstrated sufficiently to warrant going ahead with full approval right now, in our view, with regards to the risks that are involved.

So before we adjourn, are there any last comments from the FDA?

(No response.)

Adjournment

DR. HOFFMAN: Okay. If not, then I think we'll adjourn the meeting.

I want to thank everyone for their careful preparation and participation. I think this was very stimulating and informative, and we'll look forward to seeing what the next analyses will bring. Thank you very much.

(Whereupon, at 2:35 p.m., the meeting was adjourned.)